American Heart Journal

VOL. 33 APRIL, 1947 NO. 4

## Original Communications

# OBSERVATIONS ON THE VOLUME OF THE PULMONARY CIRCULATION AND ITS IMPORTANCE IN THE PRODUCTION OF CYANOSIS AND POLYCYTHEMIA

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EVER since the classical studies of Lundsgaard and Van Slyke,[1] pulmonary factors have been recognized to be of great importance in the production of cyanosis. Cournand and Richards,[2] in a recent report, have analyzed the mechanism of the exchange of oxygen and carbon dioxide in the ventilation of the blood in its passage through the lungs. Little attention, however, has been directed to the volume of blood reaching the lungs for aeration.

The operation developed by Blalock and Taussig[3] for the surgical treatment of pulmonary stenosis and atresia offers a unique opportunity to study the effect of increasing the circulation to the lungs in persons suffering from marked reduction in the pulmonary blood flow. The results of the operation demonstate that, in a person with a congenital malformation of the heart of such a nature as to cause significant reduction in the pulmonary blood flow, both cyanosis and polycythemia are greatly diminished by increasing the circulation to the lungs. Since the importance of the volume of blood flow to the lungs in the production of cyanosis and polycythemia has not heretofore been demonstrated, a brief report on this aspect of the work is warranted.

In our first report,[3] Cases 2 and 3 illustrate the extraordinary effect upon the oxygen saturation of the arterial blood which results from an increased pulmonary flow. In Case 2 the oxygen saturation of the arterial blood rose from 36.3 per cent to 73.8 per cent in the first ten days after operation and then gradually rose to 86.7 per cent. During this time the red blood cell count fell from

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Aided by a grant from the Commonwealth Fund.
Received for publication Aug. 22, 1946.

7.6 million to 5.7 million and subsequently to 4.9 million. There was a corresponding fall in the hemoglobin and in the hematocrit. The hemoglobin level fell from 24 Gm. to 17.5 Gm. and finally to 15.5 Gm.; the hematocrit reading declined from 78 to 55 and finally to 39. Similar changes were seen in Case 3: during the first three weeks after operation the oxygen saturation of the arterial blood rose from 35.5 per cent to 83.8 per cent and the red blood cell count dropped from 10 million to 6 million; the level of the hemoglobin fell from 26 Gm. to 20 Gm., and the hematocrit from 81 to 54. At the end of the second postoperative month the red blood cell count was 5.5 million, the hemoglobin 13.8 Gm., and the hematocrit 44.

These changes have been repeatedly demonstrated in successive operations. In cases in which the subclavian artery has been used for the anastomosis the degree of improvement has varied with the size of the subclavian artery and the severity of the preoperative condition. In every successful operation in which the innominate artery was used for the anastomosis there has been sufficient increase in the circulation to the lungs to demonstrate clearly the effect of adequate circulation to the lungs. Table I shows the changes in the oxygen content, the oxygen capacity, and the oxygen saturation of the arterial blood, also the red blood cell count, the hemoglobin, and the hematocrit reading in the first twelve cases in which an end-to-side anastomosis between the innominate artery and one of the main branches of the pulmonary artery has been successfully performed and the patients have been followed for at least three months thereafter.

In each instance the operation led to a considerable rise in the oxygen saturation of the arterial blood. In only one instance (Case 5) was there a fall in the oxygen content of the arterial blood. In all the other cases there was a definite rise in the oxygen content of the arterial blood, and in the four cases (Cases 4, 7, 11, and 12) in which the oxygen content of the arterial blood was extremely low there was a marked rise. In every instance in which the oxygen capacity of the arterial blood was abnormally high there was a fall in the oxygen capacity following operation. This fall roughly paralleled the decrease in the hematocrit and in the hemoglobin. These changes occurred more rapidly than did the decline in the red blood cell count. During the ensuing three weeks to one month after operation the oxygen capacity continued to fall and the oxygen saturation to rise, and the red blood cell count, the hemoglobin, and the hematocrit declined. It is a striking fact that it took over a month, usually between two and three months, for the red blood cell count to return to normal.

In Case 7 (that of an infant) there was anemia instead of polycythemia. This infant suffered from an extreme degree of anoxemia. The oxygen content was but 3.01 volumes per cent and the oxygen capacity but 14.6 volumes per cent. The operation caused an increase both in the oxygen content and in the oxygen capacity. The oxygen content rose faster than did the oxygen capacity with the result that there was a definite increase in the oxygen saturation. It is worthy of note that in this instance the oxygen content and the oxygen capacity continued to rise over a period of two months, whereas there was but little increase in the red blood cell count between the second week and the eighth week.

In this series of cases the first postoperative determinations of the oxygen content of the arterial blood were not made until ten days after operation. Nevertheless, the immediate and dramatic improvement in the color of the patient's lips which occurs just as soon as blood is permitted to flow through the new channel to the lungs indicates that these changes begin just as soon as the circulation to the lungs is increased. This clinical impression is substantiated by the few determinations which have been made at the end of the operation after the patient has been breathing air for seven minutes. In one case the oxygen content of the arterial blood rose from 7.5 to 14.5 volumes per cent, the oxygen saturation rose from 30.1 to 69.0 per cent, and the oxygen capacity fell from 25 to 21 volumes per cent. The red blood cell count and the hemoglobin and the hematocrit fell slightly. In another case the oxygen content rose immediately from 6.1 to 18.5 volumes per cent and the oxygen saturation rose from 23.6 to 63.4 per cent.

It is worthy of note that in every instance, although the oxygen saturation of the arterial blood rose significantly, it never reached the normal value of 94 to 97 per cent saturation. This is to be expected because in every instance of tetralogy of Fallot there is some degree of over-riding of the aorta; therefore the aorta always receives some venous blood from the right ventricle. Indeed, the difference between the oxygen saturation of the normal person and the oxygen saturation attained in these cases probably indicates the relative volume of venous blood shunted into the systemic circulation in the presence of adequate circulation to the lungs.

The second significant finding is that even though the oxygen saturation of the arterial blood never reaches the normal value, it appears that in the presence of adequate circulation to the lungs an oxygen saturation of 70 to 88 per cent is sufficiently high to remove the stimulus which leads to the development of compensatory polycythemia. This is shown by the fact that over a period of weeks there is a steady decline in the hemoglobin, the red blood cell count, and the hematocrit, and finally after a period of several months these values have returned to normal.

Additional studies on patients who have come to the Harriet Lane Home for investigation of various cardiac abnormalities have shown that some children with minimal disability may suffer from relatively severe anoxemia. These children have no polycythemia and show slight cyanosis of the nail beds but have lips of normal color. They are able to run and play as other children do. In a group of such children in whom the cyanosis was due to a venous-arterial shunt, the oxygen saturation of the arterial blood was between 66 per cent and 75 per cent. This is exactly what is to be expected on a theoretical basis, for it has long been known that it requires 5 Gm. of reduced hemoglobin in the circulating blood to cause "visible" cyanosis; hence, if there are 15 Gm. of hemoglobin it means that one-third of the blood in the capillaries must be in the reduced form to cause "visible" cyanosis. Nevertheless, it is a striking fact that in young children, if the oxygen saturation of the arterial blood remains above 66 per cent, there is no need for a compensatory polycythemia. This is a far lower level of

TABLE I. THE EFFECTS OF AN ARTIFICIAL DUCTUS ARTERIOSUS ON THE ARTERIAL OXYGEN SATURATION, AND THE RED BLOOD CELL COUNT, HEMOGLOBIN, AND HEMATOCRIT READING OF PATIENTS WITH A TETRALOGY OF FALLOT

| CASE | NAME | TIME INTERVAL | ARTERIAL OXYGEN CONTENT (VOLUMES PER CENT) | OXYGEN CAPACITY (VOLUMES PER CENT) | ARTERIAL OXYGEN SATURATION (VOLUMES PER CENT) | RED BLOOD CELL COUNT (MILLIONS) | HEMOGLOBIN (GM.) | HEMATOCRIT READING |
|---|---|---|---|---|---|---|---|---|
| 1 | B. R. | Preoperative | 11.7 | 32.3 | 36.3 | 7.5 | 24 | 71 |
| | | 9 days postoperative | 20.3 | 27.5 | 73.8 | 6 | 19 | 61 |
| | | 26 days* | 19.8 | 23.9 | 82.8 | 6 | 17.5 | 55 |
| | | 5 months | 17.6 | 20.3 | 86.7 | 4.9 | | 39.6 |
| 2 | M. M. | Preoperative | 10.7 | 30.2 | 35.5 | 10 | 26 | 81 |
| | | 9 days postoperative | 17.7 | 22.2 | 79.7 | 6.2 | 20 | 54 |
| | | 24 days | 17.7 | 21.1 | 83.8 | 6 | 20 | 53 |
| | | 2½ months | | | | 5.5 | 13.8 | 44 |
| 3 | J. B. | Preoperative | 13.3 | 29 | 45.9 | 9.9 | 20.7 | 84 |
| | | 2 weeks postoperative | 16.5 | 22.0 | 75.6 | 7.1 | 17.2 | 56 |
| | | 4 weeks | 16.6 | 21.4 | 77.5 | 6.2 | 14 | 44 |
| | | 3 months | 13.3 | 17.9 | 79.3 | 5.3 | 13 | 37 |
| 4 | J. R. | Preoperative | 4.7 | 22.9 | 20.5 | 8.1 | 22 | 66 |
| | | 9 days postoperative | 13.3 | 20.4 | 65 | 7.3 | 16.5 | 55 |
| | | 3 weeks | 13.1 | 19.5 | 67 | 5.4 | 14 | 53 |
| | | 7 months | 15.4 | 21.1 | 73 | 5.2 | | 53 |
| 5 | J. S. | Preoperative | 19.0 | 28.9 | 65.8 | 8.0 | 23.2 | 82 |
| | | 10 days postoperative | 18.0 | 22.6 | 79.5 | 6.5 | 16.5 | 66 |
| | | 6 weeks | 17 | 20 | 85 | 5.5 | 14.3 | 20 |
| | | 7 months | 16.8 | 20.0 | 84.0 | 5.2 | 17.6 | 43.6 |
| 6 | L. S. | Preoperative | 11.3 | 29.3 | 38.6 | 9.9 | | 91 |
| | | 10 days postoperative | 12.9 Crying | 20.1 | 64.0 | 6.5 | | 38.2 |
| | | 6 weeks | 15.7 Crying | 21.2 | 74 | 5.2 | | 52.9 |
| | | 9 months | 16.0 Quiet | 19.4 | 82.6 | 4.3 | | 40 |

*All determinations are postoperative values except the initial ones which are marked preoperative.

TABLE I. THE EFFECTS OF AN ARTIFICIAL DUCTUS ARTERIOSUS ON THE ARTERIAL OXYGEN SATURATION, AND THE RED BLOOD CELL COUNT, HEMOGLOBIN AND HEMATOCRIT READING OF PATIENTS WITH A TETRALOGY OF FALLOT (Cont'd)

| CASE | NAME | TIME INTERVAL | ARTERIAL OXYGEN CONTENT (VOLUMES PER CENT) | OXYGEN CAPACITY (VOLUMES PER CENT) | ARTERIAL OXYGEN SATURATION (VOLUMES PER CENT) | RED BLOOD CELL COUNT (MILLIONS) | HEMOGLOBIN (GM.) | HEMATOCRIT READING |
|---|---|---|---|---|---|---|---|---|
| 7 | M. C. | Preoperative | 3.01 | 14.6 | 20.6 | 5.7 | 14 | 45 |
| | | 2 weeks postoperative | 8.39 | 17.6 | 47.7 | 6 | 14 | 42.5 |
| | | 2 months* | 13.8 Crying | 21.4 | 64.5 | 6.2 | 16.4 | 53.3 |
| | | 6 months | 11.6 Crying | 19.7 | 58.9 | 6.3 | 15.8 | 48.5 |
| 8 | J. P. | Preoperative | 15.4 | 31.5 | 48.9 | 8.7 | 24.6 | 67.7 |
| | | 2 weeks postoperative | 17.0 | 22.0 | 77.2 | 5.9 | 17.5 | 54.9 |
| | | 3 months | 16.6 | 21.5 | 77.2 | 5.8 | 15.2 | 49.5 |
| 9 | P. R. | Preoperative | 13.7 | 29 | 47.2 | 10.9 | 23.5 | 67.8 |
| | | 10 days postoperative | 14.2 | 21.2 | 67.0 | 6.6 | 15.1 | 55.6 |
| | | 3 weeks | 14.8 | 22.8 | 65 | 7.3 | | 58.9 |
| | | 2 months | 16.8 | 23.4 | 71.5 | 7.9 | 19.6 | 58.3 |
| 10 | R. W. | Preoperative | 16.9 | 30.7 | 55.1 | 9 | 25.5 | 82.8 |
| | | 10 days postoperative | 16.2 | 23.2 | 69.8 | 6.4 | | 63 |
| | | 3 weeks | 18.9 | 25 | 75.6 | 7.4 | 19 | 68.3 |
| 11 | P. L. | Preoperative | 7.3 | 25.4 | 28.7 | 8.8 | 20.4 | 71 |
| | | 10 days postoperative | 14.5 | 19.3 | 75.2 | 6.4 | 12.8 | 56.7 |
| | | 2 weeks | 13.6 | 19.5 | 69.8 | 7 | | 54.8 |
| | | 10 weeks | 16.9 | 21.8 | 77.6 | 6.9 | 15.4 | 56.8 |
| 12 | A. B. | Preoperative | 7.5 | 25 | 30.1 | 6.4 | | 55.1 |
| | | 2 weeks postoperative | 14.8 | 17.5 | 84.1 | 5.2 | | 41.6 |
| | | 3 months | 13.9 Crying | 16.3 | 85.3 | 4.6 | | 38.6 |

oxygen saturation than the normal person can tolerate. The mechanism by which these children are enabled to adjust to this degree of oxygen unsaturation is under investigation.

We do not mean to imply that the lack of circulation to the lungs is the sole cause for the production of cyanosis and polycythemia, or that in the presence of polycythemia all of the blood which passes through the lungs is in effective contact with the oxygen in the alveolae. On the contrary, the change in the patient's color when he is anesthetized and is receiving high concentrations of oxygen, offers clear evidence that without any fundamental alteration in the course of the circulation the oxygen saturation of the arterial blood may be greatly increased. In an attempt to analyze these factors, samples of arterial blood have been obtained prior to operation but after the patient was anesthetized and was receiving oxygen in high concentration. These samples have shown a striking increase in the oxygen saturation due to an increase in the oxygen content of the arterial blood, but, as is to be expected, there was no change in the oxygen capacity. These samples are truly basal, a condition which it is virtually impossible to obtain during an arterial puncture made when a child is conscious. These values are probably influenced both by the inhalation of a high concentration of oxygen and by the basal condition associated with anesthesia, and possibly by the anesthetic agent. The relative importance of these factors is not easy to determine. Nevertheless, the fact that there is a rise in the oxygen saturation of the arterial blood when the patient is given a high concentration of oxygen is in accord with the existence of pulmonary factors emphasized by Lundsgaard and Van Slyke[1] in their classical studies on cyanosis.

Furthermore, we have seen a number of patients in whom there was cyanosis and polycythemia in the presence of adequate or excessive circulation to the lungs. A heart of the Eisenmenger type is an excellent example. The cause of the cyanosis in these patients is by no means clear. In such individuals there may well be some alteration in the pulmonary epithelium or in the pulmonary vascular bed which prevents complete oxygenation of the blood in its passage through the lungs.

It is important to remember that excessive pulmonary circulation places a strain on the heart. This fact has been clearly demonstrated by the benefit derived from the ligation of a large patent ductus arteriosus. Therefore, the desired objective in the surgical treatment of pulmonary stenosis is *adequate*, not excessive, circulation to the lungs. By "adequate" is meant a sufficient volume of blood to remove the stimulus for polycythemia and to raise the oxygen saturation of the arterial blood to the level which permits full or reasonably full activity to the patient without placing an undue strain on the heart. It is hoped that sufficient pulmonary circulation can be established to raise the oxygen saturation of the arterial blood to or above the threshold of "visible" cyanosis and to enable the red blood cell count, the hemoglobin, and the hematocrit to return to and remain within normal limits. Recent experience shows that, in the majority of children, these results can be attained by the anastomosis of the subclavian artery to the pulmonary artery. Furthermore, in many instances,

the anastomosis of the subclavian artery to the pulmonary artery has caused no demonstrable cardiac enlargement. Obviously, if such results can be attained by the use of the smaller vessel, the employment of the subclavian artery is preferable to that of the innominate artery.

## CONCLUSIONS

Diminished blood flow to the lungs, such as occurs in the tetralogy of Fallot, causes unsaturation of the arterial blood. When this is extreme and persistent, the condition leads to the development of polycythemia.

In patients in whom the cyanosis and polycythemia result from lack of adequate circulation to the lungs, increasing the circulation to the lungs increases the oxygen saturation of the arterial blood, lessens the cyanosis, and leads to a reduction in the polycythemia.

An oxygen saturation of 75 to 88 per cent can usually be attained in patients with a tetralogy of Fallot by an anastomosis of the proximal end of the innominate artery to the side of one of the pulmonary arteries. At such a level of oxygen saturation of the arterial blood the stimulus for the production of polycythemia has been withdrawn.

An oxygen saturation of 65 to 70 per cent may be sufficient to enable the child to indulge in unrestricted activity and does not necessarily lead to the development of polycythemia.

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# STUDIES ON THE CORONARY CIRCULATION

## II. The Collateral Circulation of the Normal Human Heart by Coronary Perfusion With Radioactive Erythrocytes and Glass Spheres

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### INTRODUCTION

DESPITE the accumulation of considerable material on the coronary circulation during the past 250 years, many questions still remain to be answered. Although it was in 1708 that Thebesius[1] first demonstrated by careful dissection the occurrence of anastomoses between both coronary arteries, the existence of intercoronary arterial anastomoses in normal hearts has been a point of dispute up to the present time. There have been two sharply divergent opinions about this question. First, there are those whose investigations have led to the conclusion that the coronary arteries in normal hearts are end-arteries, and that no anastomoses other than capillaries normally exist. Hyrtl[2] in 1855, on the basis of injection and corrosion experiments, denied the existence of coronary arterial anastomoses, and in 1866 Henle[3] confirmed his work. As the result of their experiments on the clamping of coronary arteries in curarized dogs, Cohnheim and von Schulthess-Rechberg[4] in 1881 stated that the coronary arteries were end-arteries. More recently, Blumgart, Schlesinger, and Davis[5] stated that anastomoses larger than 40 micra in diameter are not found in normal hearts, and that these fine intercoronary communications are not of functional significance in obviating the untoward results of rapidly developing coronary narrowing or occlusion. Their method of study, developed by Schlesinger[6] in 1938, consisted of the injection of a radiopaque lead-agar mass into the coronary arteries followed by unrolling of the heart so that all of the coronary arteries could be visualized in one plane by roentgenography. The filled coronary tree was carefully dissected with the aid of an x-ray of the radiopaque vessels. The lead-agar perfusate regularly penetrated to all vessels 40 micra in diameter, reached about 50 per cent of vessels 20 micra in diameter, and never entered vessels smaller than 10 micra in diameter. When this material was injected into one of the coronary arteries, they were unable to demonstrate its presence in the opposite coronary artery in normal hearts. They therefore concluded that intercoronary anastomoses larger than 40 micra in diameter are not found,

From the Research Laboratory Cedars of Lebanon Hospital.
Read at the Second Inter-American Congress of Cardiology, Mexico City, Oct. 5-12, 1946.
Endowed by grants from the Beaumont and Blanche May Funds.

and that anastomotic communications measuring less than approximately 40 micra in diameter exist between the coronary arteries of normal hearts. However, in pathologic hearts, their conclusions were as follows: "Obstruction to normal coronary arterial blood flow by arteriosclerotic narrowing or occlusion regularly results in the development of intercoronary anastomoses measuring 40 to 200 micra in diameter. Anastomotic circulation develops, then, only when and where it is needed. The development of such anastomoses is not related to age, for they are not present in the hearts of even senile patients when little or no coronary arteriosclerosis is present." Another significant conclusion was that anastomoses over 40 micra in diameter occurred in hypertrophied hearts even in the absence of coronary artery disease.

Employing the same method of study, Ravin and Geever[7] confirmed the work of Blumgart and co-workers by finding interarterial anastomoses, in the absence of coronary occlusion, in only 21 hearts in a series of 166 hearts studied. In these hearts in which anastomoses were demonstrated, they did not state the condition of the coronary arteries or the size and weight of the heart.

On the other hand, a great body of evidence supporting the existence of intercoronary arterial anastomoses has been accumulated by many investigators, culminating in the classical anatomic studies of Spalteholz and of Gross. Employing methods consisting of the injection of colored or radiopaque gelatin solutions into the coronary arteries, with clearing of the remaining tissues, followed by dissection and roentgenography of the intact heart, Spalteholz[8] in 1907, and Gross[9] in 1921, reached the following conclusions: (1) No end-arteries exist in the heart; (2) anastomoses exist between the branches of each coronary artery; (3) anastomoses exist between the right and left coronary arteries both in their capillary as well as precapillary distribution; (4) anastomoses exist between the coronary arteries and vessels from the adjacent and attached organs; (5) anastomoses in the heart are universal and abundant. Furthermore, these observers felt that coronary anastomoses increased with age. Gross emphasized that the development of septal anastomoses and rami telae adiposae (vessels lying in the fatty tissue under the visceral pericardium) begins in the second decade of life and reaches its maximal development in the seventh decade of life.

In 1942, Prinzmetal, Kayland, Margoles, and Tragerman[10] published a quantitative method for determining collateral coronary circulation in human hearts obtained post mortem. Adapting Dock's kerosene perfusion method,[11,12] they perfused kerosene through both coronary arteries under constant pressure, and the flow through each artery was measured. Then, one of the coronary arteries was suddenly occluded by a clamp just above the cannula, and the flow through the opposite coronary artery was measured. If the flow through the unobstructed vessel increased, then the increase in flow must have necessarily been due to fluid going through the collateral circulation. That is, the increase in the volume of fluid flowing through the unobstructed coronary artery represented that amount of fluid flowing into the vascular tree of the opposite side of the heart distal to the occluded coronary artery, via the available anastomotic channels present. Thus, the percentage of collateral circulation could be meas-

ured. Collateral circulation which averaged 4.16 per cent was found in all but one of twelve normal human hearts. The average collateral flow from the left to the right coronary artery was 19.2 c.c. per minute or 4.55 per cent of the flow through the left coronary artery, while the average flow from the right to the left coronary artery was 6.2 c.c. per minute or 4.05 per cent of the flow through the right coronary artery. It was also found that if a radiopaque gelatin mixture with a viscosity slightly greater than blood was injected into one coronary artery, it regularly appeared at the opposite coronary artery in normal hearts of persons ranging from 3 to 67 years of age. The entire coronary arterial tree was filled as was demonstrated by roentgenography. If this same radiopaque substance was injected into either the anterior descending or the circumflex branch of the left coronary artery, the entire coronary artery tree was also filled.

The fact that the problem of the existence of interarterial anastomoses in the human heart is still unsettled, despite much good work by careful and reliable investigators, has prompted us to seek new methods of study in an effort to cast more light on this controversial subject. A quantitative method for the determination of collateral flow was presented in 1942.[10] In this paper are presented two new methods for the study of the collateral circulation of the heart which help to solve these problems.

## STUDIES WITH PERFUSION OF RADIOACTIVE RED CELLS

Human radioactive red cells were perfused through either the anterior descending branch or circumflex branch of the left coronary artery, and the

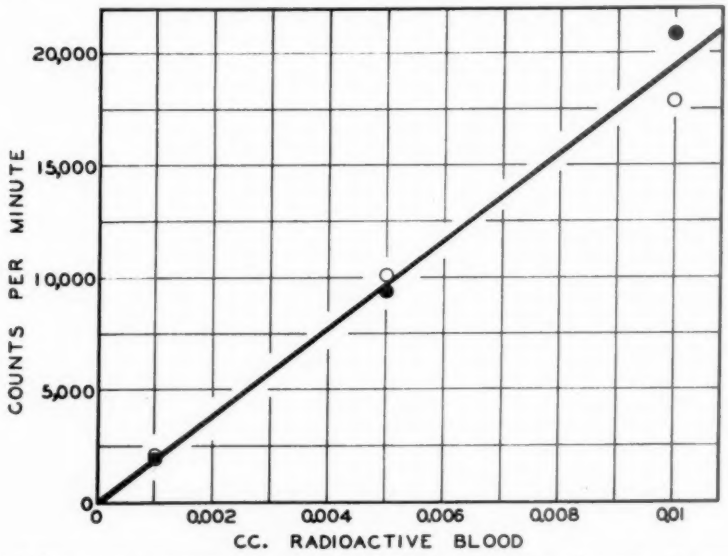



**Fig. 1.—Geiger count measurements of various dilutions of radioactive red cells prepared with P32. This red cell suspension was the fluid perfused through the coronary artery in the perfusion experiments. It can be seen that 0.001 c.c. of the red cell suspension was easily measured by the Geiger counter. If larger amounts of radioactive phosphorus are used, it should be possible to detect even smaller volumes of the erythrocyte suspension. The dots and circles represent separate determinations of thin films prepared on glass slides with 0.01 c.c. volumes of erythrocyte suspensions.**

distribution and concentration of these erythrocytes were measured in various areas of the ventricular myocardium. This method was utilized because it has the following advantages over the classical techniques for the study of the coronary circulation which involve the injection of radiopaque or colored materials: (1) Since the erythrocytes are labelled, their distribution and concentration throughout the heart can be quantitatively determined; (2) blood is the normal circulatory fluid and is therefore always preferable to other nonphysiologic fluids in studies of the circulatory system; (3) very small amounts of blood containing radioactivity can be measured. This is illustrated in Fig. 1.

*Method.*—Human hearts were obtained at necropsy, all post-mortem examinations having been performed within twenty-four hours after death. Some hearts were kept in a refrigerator at 4°C. for approximately eighteen hours before the experiment was conducted, and others were perfused immediately following autopsy. Prior to perfusion these hearts were incubated in normal saline solution at 40°C. for one-half to one hour in order to overcome rigor mortis. A glass cannula was then placed and securely tied in either the anterior descending branch or the circumflex branch of the left coronary artery. The right coronary artery and coronary sinus were similarly cannulated. Heavy clamps were applied over the auricles, pulmonary artery, and pulmonary veins in order to prevent leakage from the ventricular cavities and to cut off the circulation to the auricles. Cotton plugs were placed in the pulmonary artery and the aorta at the level of the semilunar valves in order to prevent contamination of the contents of the ventricular cavities from leakage of the perfusate.

Human red blood cells were made radioactive by incubation with radioactive phosphorus (P32 in the form of $Na_2HPO_4$) as described by Nylin and Malm.[13] The amount of P32 used for incubation in each experiment varied from 0.5 to 1.0 millicurie per 100 c.c. of a suspension containing equal volumes of erythrocytes and normal saline. The erythrocyte suspension was equilibrated with alveolar air, and incubated at 37°C. for two hours. The red cells were packed down by centrifugation and the supernatant fluid was decanted. Then the red cells were washed with saline two or three times, until the supernatant fluid was practically free of radioactivity. The final composition of the perfusate consisted of equal volumes of labelled red cells and normal saline. If the red cells were packed down by centrifugation at this point it was found that the supernatant fluid had approximately one-eighteenth to one-thirtieth the radioactivity of the cells, depending upon the number of previous washings.

This radioactive erythrocyte-saline fluid was perfused through either the anterior descending branch or the circumflex branch of the left coronary artery at a constant pressure of 100 mm. Hg until the perfusate was seen to issue from the coronary sinus; this usually occurred after only 10 c.c. of blood had been perfused. The total amount of fluid perfused through the heart in each experiment varied from 30 to 90 c.c. and the perfusion was completed in thirty to sixty seconds. The heart was then unrolled in the manner described by Schlesinger,[6]

and the distribution of the radioactive erythrocytes was determined by means of (1) Geiger counts at various arbitrarily chosen sites on the endocardial and pericardial surfaces of the heart, and (2) by exposing the heart to x-ray film for fifteen to forty-eight hours, thereby obtaining a radioautograph. The heart was placed on a sheet of Pliofilm to protect the photographic plate from wetting. The shadow on the exposed plate was produced by the beta rays of the radiophosphorus in the erythrocytes. The intensity of the shadow was proportional to the amount of blood in all areas and was found to correlate fairly well with the results obtained by the Geiger counts in the corresponding areas (Figs. 3 and 5). In every experiment counts were made on known volumes of the perfusion fluid. One-hundredth of a cubic centimeter of perfusate measured with a micropipette represented the standard used. By calibrating the radioactivity of a known amount of perfusate, the amount of blood in each area could be determined.

All Geiger count measurements of the heart were made under the following conditions. The heart was placed on a lead plate one-fourth inch in thickness.

**Fig. 2.—Radioautograph. A 62-year-old man died of uremia due to chronic pyelonephritis. Heart exhibits minimal coronary arteriosclerosis. Radioactive erythrocyte suspension was perfused through circumflex branch of left coronary artery. Exposure to x-ray film was twenty-four hours. Heart was unrolled so that all of the coronary arteries lay in one plane. The outlines of the right coronary artery and its posterior descending branch can be seen. The entire left ventricle is well filled with blood. Radioactive erythrocytes are present in all parts of the right ventricle but in lesser amounts than in the left ventricle. The interventricular septum, which was cut out, is well filled with radioactive red cells.**

***L. A.*, left auricle; *R. A.* right auricle; *L. V.*, left ventricle; *R. V.*, right ventricle; *I.V.S.*, interventricular septum; *R. Descending*, posterior descending branch of right coronary artery.**

The area to be measured was placed over a hole in the lead plate which was 1.8 cm. in diameter. The upper surface of the lead plate was 13 mm. above the window of the Geiger counter tube. In this way, the only area that would be measured was that placed over the hole, since the lead plate blocked all beta rays emitted from the rest of the heart. Since beta rays are readily absorbed by tissue, the radioactivity contained in only a 7 mm. depth of tissue was actually measured.

*Results.*—Perfusion with radioactive red cells was performed on seven normal hearts obtained from patients ranging in age from the newborn infant to 73 years. In all instances the entire left ventricle and septum were well filled with blood. Radioactive red cells were also demonstrated in all parts of the right ventricle, although in lesser concentrations, in every one of these hearts. Radioautographs and measurements of radioactivity expressed in terms of red blood cell equivalents showing these findings are illustrated in Figs. 2 to 6.

**Fig. 3.—Radioautograph. A 50-year-old woman died of bronchogenic carcinoma. Heart normal. Fifty cubic centimeters of radioactive red cells suspension were perfused through the circumflex branch of the left coronary artery at 100 mm. Hg pressure. Perfusion completed in 30 seconds. At completion of perfusion with radioactive erythrocytes, a radiopaque solution was injected into the right and left coronary arteries so that the outlines of the major coronary arteries could be seen by x-ray. The course of these arteries has been superimposed upon the radioautograph for purposes of orientation. Pericardial surface exposed to x-ray film for fifteen hours. The intensity of the shadows in the radioautograph is proportional to the amount of labelled erythrocytes and correlates well with the measurements obtained with the Geiger counter in the corresponding areas.**

*L. V.*, left ventricle; *R. V.*, right ventricle; *I. V. S.*, interventricular septum; *R. C.* right coronary artery; *L. Circ.*, circumflex branch of left coronary artery; *L. A. D.*, anterior descending branch of left coronary artery.

These observations are striking in that they illustrate how abundant amounts of labelled erythrocytes are distributed throughout the entire heart within a matter of a few seconds following perfusion of a comparatively small volume of blood

Fig. 4.—Radioautograph of heart of full-term baby who died at birth of asphyxia. Normal heart. Radioactive erythrocyte suspension perfused through left coronary artery. Heart exposed to x-ray film for forty-eight hours. This film was overexposed. However, this film illustrates that the whole heart was well filled with labelled erythrocytes indicating abundant anastomotic channels between the left and right ventricles present at birth.

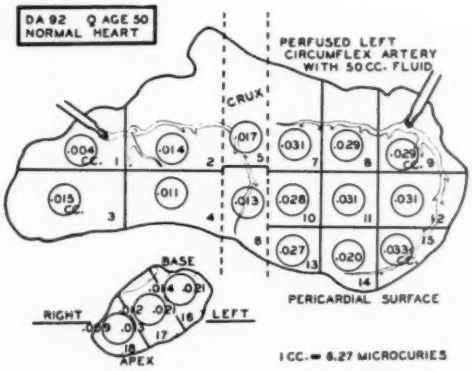



Fig. 5.—Diagram of the volume of radioactive red cells present on the pericardial surface of various areas measured throughout the right and left ventricles. This is the same heart which is shown in Fig. 3 as a radioautograph. Areas numbered *1* to *4* are in right ventricle. Areas *5* and *6* are located at the posterior aspect of the interventricular septum. Areas *7* to *15* are in left ventricle. The course of the right and left coronary arteries are sketched in. Areas *16*, *17*, and *18* are in the interventricular septum with measurements taken of the right and left surfaces of the septum respectively. The measurements clearly show that the perfused erythrocytes fill the entire left ventricle. They are also present in the right ventricle but in lesser amounts. There were greater amounts of red cells on the left surface of the septum than on the right.

The volumes of erythrocytes recorded are red cell equivalents of radioactivity.

through one of the branches of the left coronary artery. These findings are all the more significant when it is considered that 30 to 50 c.c. of blood is an insufficient volume to fill all the vessels in the heart. Since these red cells can easily pass into any part of the left ventricle, the presence of numerous anastomosse in the left ventricle is indicated. A collateral circulation between the left and right ventricle is demonstrated by the detection of labelled erythrocytes throughout the right ventricle.

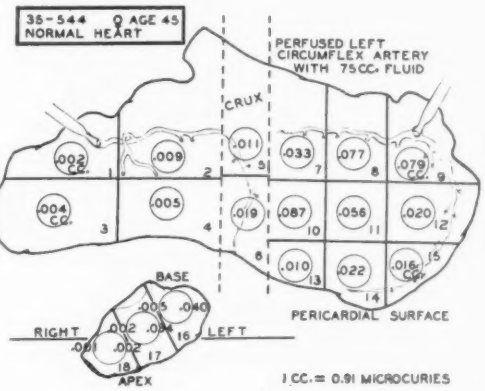



Fig. 6.—Diagram of the volume of radioactive erythrocytes present on the pericardial surface of various areas measured throughout the right and left ventricles. A 45-year-old woman died of carcinoma of the pancreas. Heart normal. Seventy-five cubic centimeters of radioactive red cell suspension were perfused through the circumflex branch of the left coronary artery at 100 mm. Hg pressure. Perfusion completed in 30 seconds. Areas numbered *1* to *4* are in right ventricle. Areas *5* and *6* are located at the posterior aspect of the interventricular septum. Areas *7* to *15* are in left ventricle. The course of the right and left coronary arteries are sketched in. Areas *16*, *17*, and *18* are in the interventricular septum with measurements taken of the right and left surfaces of the septum respectively. The measuremeats clearly show that the perfused erythrocytes fill the entire left ventricle. They are also present in the right ventricle but in lesser amounts. There were greater amounts of red cells on the left surface of the septum than on the right.

The volumes of erythrocytes recorded are red cell equivalents of radioactivity.

### *Perfusion of Glass Spheres*

Glass spheres with diameters ranging from 10 to 400 micra were suspended in a radiopaque mixture. This mixture was injected into the cannulated left coronary artery, and the spheres were recovered from the right coronary artery, coronary sinus, and right and left ventricular cavities. The diameters of these recovered beads were determined by microscopic examination with the aid of a calibrated reticule in the eye piece of the microscope. By this means the following facts could be determined: (1) the size of the largest bead recovered from each site of collection, indicating the size of the largest channels allowing the passage of the glass spheres; (2) a percentage distribution graph of the various sizes of beads recovered which could be compared with the percentage distribution of the mixture of beads which was injected. This was determined by measuring the diameters of 200 to 500 spheres.

It follows that after injecting the beads into the left coronary artery, those obtained from the right coronary artery must represent spheres that have tra-

versed channels between the left and right coronary arteries, i.e., arterio-arterial anastomoses. Beads obtained from the coronary sinus represent beads that have traversed channels between the left coronary artery and coronary sinus; i.e., arteriovenous anastomoses. Beads obtained from the right or left ventricular cavities after injection through the left coronary artery represent beads that have come through any or all of the following: arterioluminal vessels, arteriosinusoidal vessels, and Thebesian veins.

*Method.*—The hearts were obtained and prepared for perfusion in exactly the same way as in the previous experiment. The perfusing fluid consisted of glass spheres* suspended in a radiopaque mixture. Dock's radiopaque mass† was found to be the most suitable medium for suspension of the beads after many experiments with other fluids. Fluids such as kerosene, saline, 6 per cent acacia solution, 20 per cent sucrose, plasma, and blood were found to be unsatisfactory for various reasons. The final composition of the perfusate as used in these experiments was 2 Gm. of glass spheres‡ suspended in 100 c.c. of Dock's radiopaque mass.

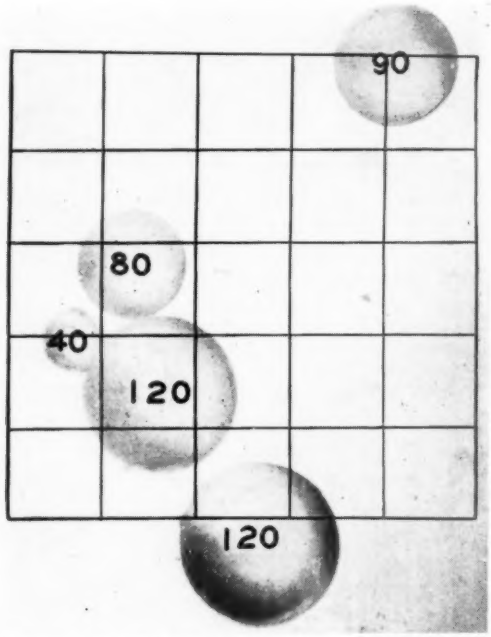



Fig. 7.—Glass spheres as seen under the microscope with reticule superimposed. Each square of reticule is 80 micra under low power. Number superimposed on sphere is diameter of sphere in micra (× 100).

The perfusate was injected into the left coronary artery by means of a 50 c.c. Luer syringe or sometimes an Asepto syringe. The pressure applied was intermittent, but never exceeded 160 mm. Hg and was usually less than this.

*Glass spheres were obtained from Prismo Products, 1211 Architect's Building, Los Angeles, Calif.
†The composition of this mass has been described in detail in a previous publication.[10]
‡One gram of beads was estimated to contain approximately 6 million spheres.

Collections of the perfusate containing the beads were then made at the cannulated right coronary artery and at the cannulated coronary sinus. At the completion of the perfusion the fluid present in each ventricular cavity was removed with a pipette after the cotton plugs in the pulmonary artery and aorta were removed.

In order to isolate the glass spheres contained in the radiopaque perfusate, the lead and mercury salts had to be dissolved chemically. First, concentrated sodium hydroxide was added to dissolve the lead carbonate. The supernatant liquid was carefully decanted and the beads were washed with distilled water three or four times. Then small amounts, about 1 c.c. each, of concentrated hydrochloric acid and nitric acid were added, and after gentle heating the mercury sulfide was dissolved. The beads were again washed several times with distilled water. Since the glass spheres are heavier than the washing fluids, they always settled to the bottom of the test tube. The clear supernatant fluid was decanted and the beads at the bottom of the tube were transferred to an ordinary glass slide with the aid of a rubber policeman. Their diameters were determined by microscopic examination with the aid of a calibrated reticule in the eye piece. The appearance of the spheres is shown in Fig. 7.

*Results.*—

*Right Coronary Artery*: Glass spheres were injected into the left coronary arteries of thirteen hearts with normal or minimally arteriosclerotic coronary arteries, obtained from patients ranging from 4 to 73 years of age. Arteries were considered to be minimally arteriosclerotic if a few flat yellowish plaques without calcification or encroachment upon the arterial lumen were present in one or more of the major coronary arteries or its branches. This was determined by careful anatomic dissection. These hearts were not hypertrophied, and none of these were obtained from patients who had clinical evidence of heart disease during life. As can be seen in Table I, glass spheres were recovered from the right coronary artery in all but two instances. In these eleven hearts, the largest spheres recovered ranged in size from 70 to 180 micra in diameter. In eight of these eleven hearts, the maximum size of the beads was 70 to 90 micra in diameter. It must be concluded that in eleven of the thirteen normal hearts measured, channels of arteriolar dimensions were present between the right and left coronary arteries. In this small series no variations with age were apparent. In a few hearts tested with either severe coronary arteriosclerosis and/or definite ventricular hypertrophy the maximum size of the beads recovered from the right coronary artery ranged from 120 to 150 micra in diameter (Table I).

*Coronary Sinus*: The findings with reference to spheres recovered from the coronary sinus were of interest. In all but one of the thirteen normal hearts beads were recovered from the coronary sinus following injection into either the left or right coronary artery. The maximum diameter of the spheres recovered ranged from 70 to 170 micra. In seven of thirteen instances the maximum size was greater than 100 micra. It is quite obvious that channels of larger magnitude than capillaries must exist between the coronary arteries and coronary veins to allow the passage of spheres of such dimensions. Therefore, the presence

TABLE I

| NO. | DIAMETERS OF PERFUSED BEADS (MICRA) | AGE | SEX | CAUSE OF DEATH | LARGEST DIAMETERS OF RECOVERED BEADS (MICRA) | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | RIGHT CORONARY | CORONARY SINUS | RIGHT VENTRICLE | LEFT VENTRICLE |
| | | | | *Normal or Minimal Coronary Arteriosclerosis* | | | | |
| 1 | 10 to 240 | 4 | M | Sarcoma of leg | 80 | 130 | 90 | 170 |
| 2 | 10 to 240 | 23 | F | Postoperative anuric uremia | 160 | 80 | 190 | 150 |
| 3 | 10 to 240 | 27 | F | Chronic ulcerative colitis | 70 | 110 | —* | —* |
| 4 | 10 to 440 | 30 | F | Thrombocytopenic purpura | 80 | 70 | 70 | 220 |
| 5 | 10 to 440 | 38 | M | Acute appendicitis with perforation | 90 | 90 | 180 | 170 |
| 6 | 10 to 240 | 40 | M | Bronchogenic carcinoma | 70 | 160 | 150 | 80 |
| 7 | 10 to 240 | 41 | M | Far advanced pulmonary tuberculosis | —† | 140 | 100 | 100 |
| 8 | 10 to 440 | 45 | F | Hepatic carcinoma | 170 | 80 | 90 | 170 |
| 9 | 10 to 240 | 60 | F | Carcinoma of cecum, pulmonary embolism | 70 | 170 | 200 | 170 |
| 10 | 10 to 440 | 65 | F | Cirrhosis of liver | 180 | —† | —* | —* |
| 11 | 10 to 240 | 67 | M | Carcinoma of stomach | 70 | 90 | 170 | 200 |
| 12 | 10 to 240 | 67 | M | Malignant lymphoma Hodgkin's type | 80 | 160 | 180 | 200 |
| 13 | 10 to 240 | 73 | M | Carcinoma of cecum | —† | 150 | 160 | 200 |
| | | | | *Moderate to Severe Coronary Arteriosclerosis* | | | | |
| 1 | 10 to 240 | 62 | M | Acute posterior wall myocardial infarction | 130 | 170 | 120 | 180 |
| 2 | 10 to 240 | 63 | F | Carcinoma of sigmoid | 150 | 170 | 160 | 160 |
| 3 | 10 to 240 | 65 | F | Arteriosclerotic heart disease, congestive failure | —‡ | 80 | 160 | 160 |
| 4 | 10 to 440 | 72 | M | Carcinoma of esophagus | 150 | 300 | 140 | 180 |
| | | | | *Ventricular Hypertrophy* | | | | |
| 1 | 10 to 440 | 39 | M | Malignant hypertension with uremia | 150 | 140 | 300 | 110 |
| 2 | 10 to 440 | 64 | M | Multiple myeloma | 120 | 160 | 160 | 230 |
| 3 | 10 to 440 | 68 | M | Rupture of abdominal aortic aneurysm | 120 | 200 | 120 | 190 |
| 4 | 10 to 440 | 70 | M | Chronic emphysema, cor pulmonale | 130 | 360 | 80 | 350 |

*None collected in this experiment.
†No beads came through.
‡Left coronary artery torn. Injected through right coronary artery.

of arteriovenous anastomoses in the human heart may be inferred. In the few pathologic hearts studied, the greatest diameters of beads obtained from the coronary sinus ranged from 80 to 360 micra.

*Right and Left Ventricles*: The maximum sizes of beads recovered from the ventricles ranged from 70 to 350 micra in diameter in both normal and pathologic hearts. Since the beads were injected into the left coronary artery they reached the ventricular cavities via three possible routes: arterioluminal vessels, arteriosinusoidal vessels, and Thebesian veins. No apparent difference was noted between the right and left ventricles.

*Percentage Distribution Graph*: Graphs illustrating the percentage distribution of beads recovered from each collecting site are illustrated in Figs. 8 to 10.

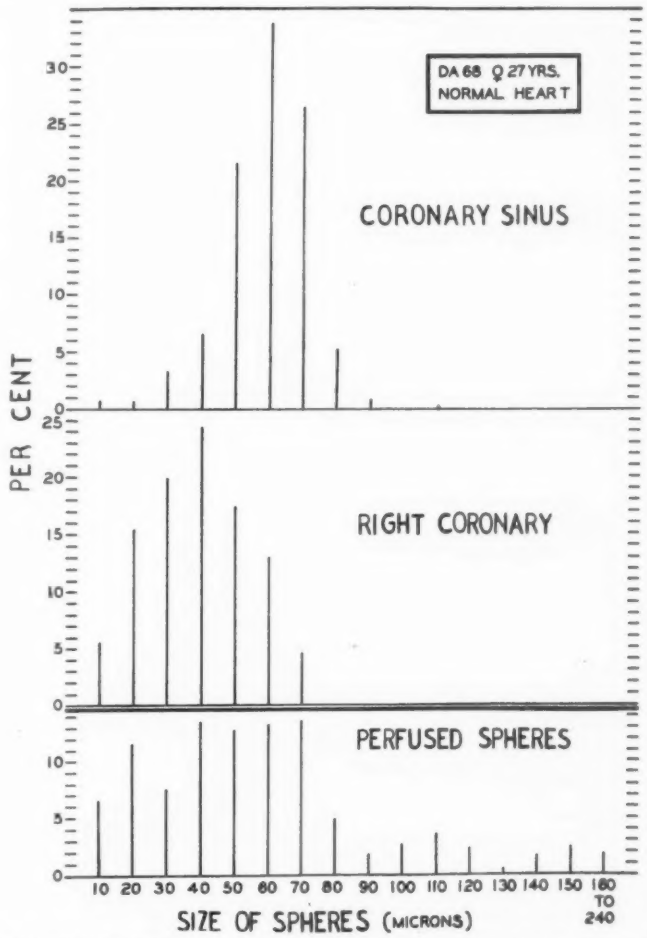



Fig. 8.— Graph showing percentage distribution of glass spheres. A 27-year-old woman died of chronic ulcerative colitis. Normal heart. One hundred and fifty cubic centimeters of radiopaque solution containing glass spheres were injected into the left coronary artery, and spheres were recovered from coronary sinus and right coronary artery. Percentage distribution of beads recovered from coronary sinus and right coronary artery compared with distribution of spheres which were perfused. In this experiment no attempt was made to collect beads from the ventricular cavities.

The number of beads of each diameter is expressed as the percentage of beads of each size in relation to the total number of spheres counted. These graphs show the diameter of the largest sphere recovered and the percentage of spheres of various sizes recovered. These do *not* show the percentage of anastomotic channels of any given diameter because many of the smaller beads may traverse larger channels. At the same time many small channels may be blocked by larger beads in the heart.

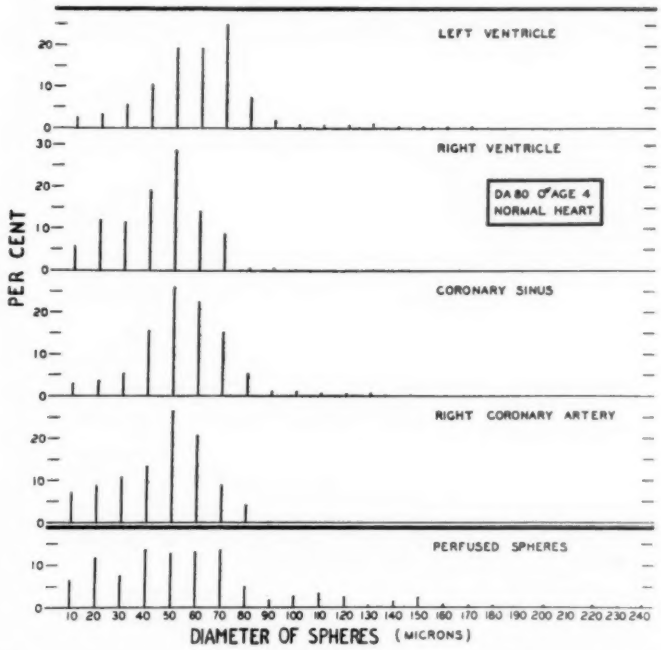



Fig. 9.—Graph showing percentage distribution of glass spheres. A 4-year-old boy died of sarcoma of the leg. Normal heart. Radiopaque solution containing glass spheres was injected into left coronary artery, and spheres were recovered from right coronary artery, coronary sinus, and right and left ventricular cavities. Relatively large anastomotic channels are present in the heart of a young individual.

When this work was begun it was thought that by knowing the percentage distribution and weight of the glass spheres injected and of those recovered it would be possible to calculate the number of anastomotic channels of various diameters present in the heart between any two points, as, for example, the number of channels of 50 micra in diameter existing between the right and left coronory arteries. Mathematically this was possible and Dr. Ernst Snapper of Los Angeles has worked out the following formula for this purpose.

Supposing a bead of size $i$ micra to be present in the fluid recovered after perfusion of the vessels, one may assume that the number of beads of size $i$ micra is proportional to the weighed sum of the vessels through which the beads may pass. Each vessel is weighted by the square of its minimum diameter.

If $N_i$ = number of vessels of diameter $i$ micra

$T_i^{i+10}$; $T_{i+10}^{i+20}$ = number of vessels whose minimum diameter ranges from $i+10$ to $i$; $i+20$ to $i+10$, where $i+10 > i$; $i+20 > i+10$

$N_i$; $N_j$; $N_k$ = per cent of beads of size $i$; $j$; $k$ micra in the fluid injected.

$P_i$; $P_j$; $P_k$ = per cent of beads of size $i$; $j$; $k$ micra in the fluid recovered.

$$\text{Then } N_i = \frac{T_{i+10}^{i+20}}{T_i^{i+10}} = \left| \frac{\frac{N_k}{N_j} - \frac{P_k}{P_j}}{\frac{P_i}{P_j} - \frac{N_i}{N_j}} \right| \left| \frac{N_i}{N_k} \right| \left| \frac{i+5}{i+15} \right|^2$$

Vessels of size up to $k$ micra play a role only if $\frac{P_j}{P_k} > \frac{N_j}{N_k}$ and the denominator of the principal formula is positive.

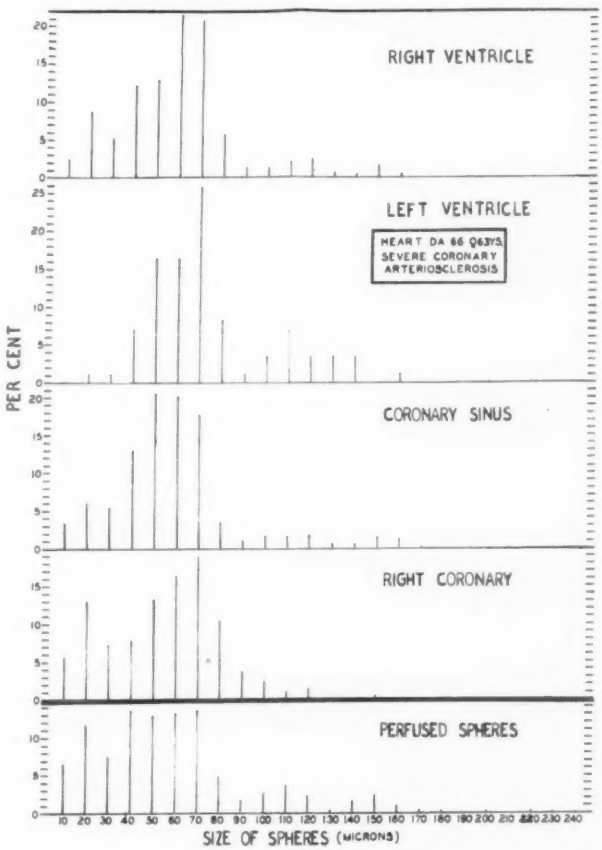



Fig. 10.—Graph showing percentage distribution of glass spheres. A 63-year-old woman died of carcinoma of sigmoid colon. Severe coronary arteriosclerosis. One hundred twenty cubic centimeters of radiopaque solution containing glass spheres were injected into left coronary artery, and spheres were recovered from the right coronary artery, coronary sinus, and right and left ventricular cavities.

We have spent a great deal of effort trying to apply this formula to our experiments. However, it was found that settling of the spheres within the heart during perfusion always occurred. Since this settling factor is obviously an inconstant one, varying not only from heart to heart but also in different vessels in the same heart, this formula could not be applied to the work herein reported. Consequently only the largest-sized anastomotic channels could be determined by the present method.

## DISCUSSION

*Methods of Study.*—Because of the difference of opinion in the literature concerning the existence of intercoronary anastomoses it was felt that a reinvestigation of the problem employing new means of approach might be fruitful, hence the introduction of the two methods of study presented in this paper.

The use of radioactive red cells as a perfusion fluid in post-mortem studies of the heart has several advantages over other perfusion media which have been used in the past, as has already been pointed out. It has been shown that the gross estimation of collateral circulation in the post-mortem heart by older methods does not approach the sensitivity achieved by the use of radioactive red cells. Therefore, these older procedures give an incomplete picture of the extent of the collateral circulation. The abundance of collateral channels present in the normal heart has not been fully appreciated. The sensitivity of labelled erythrocytes suggests its application for other studies, such as the blood supply of the normal heart valve, a much disputed problem. Nylin[13,14,15] has published some interesting studies in which radioactive blood was injected intravenously in the living patient. In this way he has been able to determine the blood volume.

One of the major deficiencies in the use of dyes and radiopaque solutions for demonstrations of the coronary circulatory bed has been that no strictly quantitative determination of the diameters of the collateral vessels has been achieved. The use of perfusates with varying viscosities and composition has resulted in varying degrees of filling of the coronary tree and its collateral channels. For example, if watery solutions or gelatin-sucrose mixtures with a viscosity slightly greater than blood are perfused through one of the coronary arteries of a normal human heart, they are seen to issue from the opposite coronary artery within a few seconds; if a lead-agar mixture with a viscosity three times greater than that of blood is so perfused, it cannot be detected by x-ray in any part of the circulatory bed of the opposite coronary artery, although the entire tree of the perfused coronary artery is well filled. Obviously, these differences are inherent in the physical properties of each of the perfusates employed. Therefore, it is difficult to accept completely any quantitative criteria as to the smallest diameters of channels through which these fluids will pass. For these reasons it was decided to perfuse glass spheres of graded size through the coronary arteries of the normal human heart. By this means one could unequivocally determine the largest diameters of collateral channels that would permit passage of the spheres. The objection may be raised that the beads were forced through these communicating vessels by the effect of the applied perfusing pressure resulting in stretching of

the lumen of the vessels. Because physiologic perfusion pressures were employed, we do not believe that this objection is a valid one. It is freely admitted, however, that measurements of the lumina of vessels in the post-mortem heart may not necessarily correspond to the actual measurements of the diameters of these vessels in life, because after death neurohumoral influences are absent; nevertheless, the post-mortem measurements are indicative of the maximum diameters these lumina are capable of attaining under appropriate circumstances.

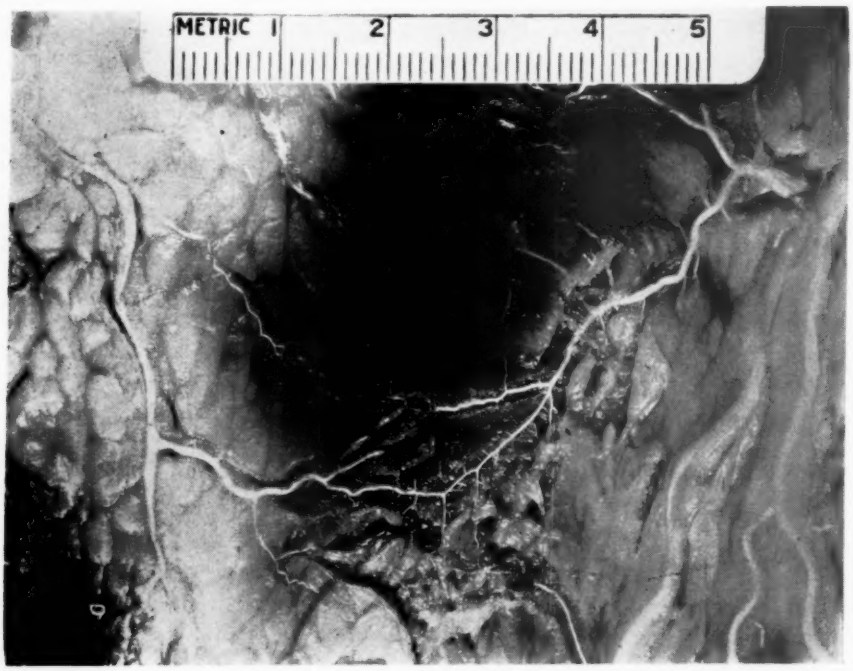
The perfusion of glass spheres of known diameters can be utilized for the study of the circulation of other organs such as the kidney, the lung, and the extremities. At present we are investigating the circulation of the kidney by this method. We had hoped to determine quantitatively the number of anastomoses of various sizes in the heart. This was mathematically possible, but because of settling of the beads within the vessels of the heart, the calculations could not be adapted to the conditions of the experiment. However, with variations in the technique this may still be possible. Possibly a perfusing fluid which will suspend the beads more evenly without settling can be found. The size of the spheres injected can be varied as desired.

In some preliminary observations,[16] living rabbits were given intravenous injections of small amounts of glass spheres without any apparent ill effects, whereas a single, large, intravenous dose resulted in convulsions and death. A few rabbits received repeated small intravenous doses over a period of two or three months without any obvious harm. When these animals were killed, the lungs were found to be packed with beads, and right ventricular hypertrophy was observed. No beads were found in any of the other viscera. It was inferred from these experiments that compensatory anastomotic channels had developed in the lungs of these animals in order for them to survive, because the total dose of beads administered to these rabbits greatly exceeded the minimal lethal dose.

*Arterio-Arterial Anastomoses.*—In the past several years most investigators have agreed that there are communicating vessels between the coronary arteries in the normal human heart but there has been no concurrence of opinion regarding their size. The present studies quantitatively measured the largest diameters of the intercoronary vessels. These channels were found to have diameters ranging from 70 to 180 micra; these diameters fall within the dimensions of arterioles. As defined by Maximow and Bloom[17] the caliber of capillaries in man averages 8 micra, whereas "the smallest arteries, 0.3 mm. in diameter or smaller are usually grouped in a separate class and are called *arterioles*." According to these definitions, our studies indicate that there are arteriolar anastomoses between the coronary arteries in the normal human heart. Dr. Clara Margoles in this laboratory has demonstrated grossly such an interarterial anastomosis in a normal heart of a 40-year-old man. By dissection this vessel was found to connect the marginal branch of the right coronary artery and the anterior descending branch of the left coronary artery. It is easy to see how relatively large spheres can pass through a vessel of such size (Fig. 11, *A*, *B*, and *C*).

In our small series of normal hearts, the diameters of the intercoronary connections did not appear to increase with age. This was also true with respect

to kerosene collateral flow measurements in normal hearts previously reported from this laboratory.[10] Blumgart, Schlesinger, and Davis[5] found no differences with increasing age in their study of normal hearts with the lead-agar perfusion method. These findings do not support the work of Gross[9] and Spalteholz[8] who found increasing anastomoses with increasing age.




*A.*

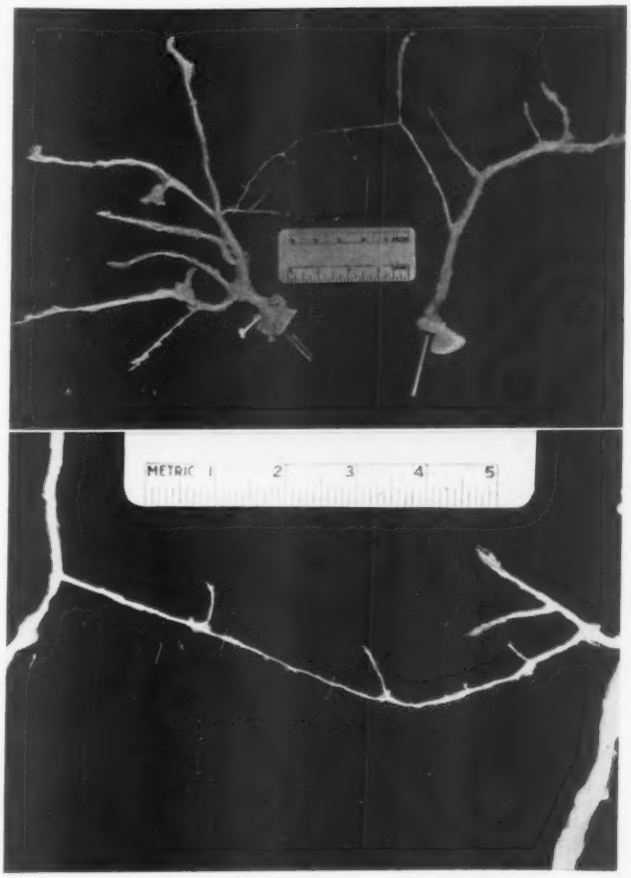
Fig. 11.—Gross anatomic demonstration of an interarterial anastomosis. The coronary arteries are filled with radiopaque gelatin solution which had been perfused through both coronary arteries.
*A*, Demonstration of an anastomosis between the marginal branch of the right coronary artery and the anterior descending branch of the left coronary artery in situ.
*B*, Demonstration of the same interarterial anastomosis after the coronary arteries were dissected away from the heart.
*C*, Magnification of *B*, illustrating that the gross diameter of the anastomosis was approximately 0.5 mm. This anastomosis is of arteriolar dimensions.

That intercoronary anastomoses increase in size in the presence of coronary arteriosclerosis or cardiac hypertrophy has been demonstrated by the work of Blumgart and associates and others. In a few such pathologic hearts our findings are entirely in agreement with their observations.

*Arteriovenous Anastomoses.*—The question of arteriovenous anastomoses in the human heart has apparently been neglected in the past. There are very few references pertaining to this important subject in the literature. In 1911, Nussbaum[18] described direct connections between arteries and veins, made up of a single layer of endothelium, possessing no muscular coat, and lying in the subendocardium. He considered these as safety outlets for arterial blood when the pressure becomes too high. Wearn[19] has stated the following: "Arteriolar-

venous communications also occur in normal hearts. They are infrequently found during a study of serial sections of the myocardium. Because of their rarity, they are probably of little importance." Hirsch[20] described vascular segments in the human heart histologically similar to vessels found in the glomus bodies of the digits; these glomus structures were arteriovenous anastomoses. He thought that these intracardiac glomus bodies functioned as "regulators between the internal arterial pressure and the interstitial pressure of the cardiac musculature acting upon the wall of the vessels."

*B.*




*C.*

**Fig. 11 (Cont'd).—For complete legend, see opposite page.**

In the present studies, relatively large glass spheres have been regularly obtained from the coronary sinus following injection into the right or left coronary artery. It is quite obvious that channels of larger magnitude than capillaries must exist between the coronary arteries and coronary veins to allow the passage of these spheres. The regular occurrence of such arteriovenous anastomoses in all hearts studied raises the question of the possible functional significance of such communications. The question is posed whether or not they

supply a mechanism to increase blood flow and provide more efficient regulation of the myocardial circulation analogous to the glomus bodies in the extremities. It is not inconceivable that such channels could allow arterial blood to supply the myocardium by (1) direct supply to the capillary bed, and (2) a shunt into the coronary veins which are connected with Thebesian vessels and capillaries. Thus, it is theoretically possible for ventricular muscle to get oxygenated blood through arteriovenous anastomoses even if a coronary artery is occluded. Unlike intercoronary anastomoses, these arteriovenous shunts should be able to function in a normal heart since the venous pressure is always less than the arterial pressure.

*Functional Significance of the Collateral Circulation.*—All of the investigations on the collateral circulation of the heart done in this laboratory during the past five years confirm the opinion of those who believe that there are extensive collateral channels of various types in the normal human heart. Most of this work has been of an anatomic nature and has not served to elucidate experimentally the physiologic significance of these vessels during life. It can only be stated teleologically that since these anastomotic communications have been demonstrated they must serve some useful function, although at present their physiologic significance is poorly understood.

Wiggers[21] has emphasized that, although intracardiac anastomoses have been anatomically demonstrated, the coronary arteries are physiologically end-arteries. With sound logic he has pointed out that the absence of pressure gradients between the coronary arteries precludes the functioning of intercoronary anastomoses in the normal heart. Although this is probably true in the case of interarterial anastomoses in the normal heart, this would not be true in regard to arteriovenous anastomoses because of the presence of an arteriovenous pressure gradient, as we have pointed out.

When one of the coronary arteries is gradually occluded, the arterial pressure distal to the narrowing or occlusion diminishes, and thus establishes a pressure gradient which now allows blood to flow from the opposite coronary artery through the existent anastomotic channels. In this way a functioning collateral circulation develops, by the enlargement of the anastomotic channels which have been shown to be present in this study. In the instance of a slowly developing coronary occlusion, this concept is not disputed and serves to explain the development of a functioning collateral circulation which has been well-demonstrated by radiopaque injection techniques and retrograde flow studies.

In this regard two other possibilities present themselves. If gradual occlusion or narrowing occurs simultaneously in both coronary arteries, there would be no pressure gradient and the function of the anastomotic channels between these arteries would therefore be limited following an occlusion of one of the coronary arteries. Another possible factor which would limit the functional capacity of intercoronary anastomoses would be the occurrence of arteriosclerosis of these channels with resulting narrowing or occlusion. Since these vessels are of arteriolar dimensions, there is no reason why arteriosclerosis can-

not occur in these locations just as in other arterioles throughout the body. We do not believe that this possibility has been heretofore appreciated, and therefore deserves further study.

When one of the coronary arteries is acutely occluded in an otherwise normal heart, are the collateral channels, which are anatomically known to exist in the normal heart, functionless? There is evidence to show that these anastomoses do function, although in a limited way. It is well known that the infarcted area in normal hearts is smaller than that supplied by the obliterated vessel. This has been demonstrated in man[22,23] and in experimental work on dogs.[24] Therefore, the rim of viable tissue around the infarct must be supplied by collateral vessels from other arteries. If a small enough artery is obstructed, collateral circulation might be sufficient to prevent myocardial necrosis.

In a previous communication[10] it was shown that if one coronary artery was suddenly occluded in a normal heart, an increase in flow in the opposite coronary artery resulted. This increase in flow was interpreted as representing the degree of collateral circulation present in the heart. Although these experiments were performed on post-mortem human hearts in which all neurohumoral influences were absent, they demonstrated the fact that collateral channels were present ready to function immediately when the need arose. There is evidence[25,26] to show that concomitant with a coronary arterial occlusion, vasoconstriction may occur in the uninvolved coronary arteries. Sectioning the stellate ganglia[27] and upper five thoracic ganglia[26] prevented a reduction in coronary flow following ligation of one of the coronary arteries. This may explain why retrograde flow is so small following coronary arterial ligation. This factor, therefore, may greatly limit the possible function of collateral channels immediately following an acute occlusion.

Eckstein, Gregg, and Pritchard[28] measured retrograde flow distal to the ligation of the descending branch of the dog's left coronary artery. Immediately following coronary occlusion the retrograde flow was nearly constant at values between 0.5 to 5.8 c.c. per minute, and then it increased very slowly after some hours to reach sizable values in a week or so. For example, the retrograde flow increased from 3.4 to 6.8 c.c. per minute within forty-eight hours, and to 18 c.c. per minute within a week. They also observed that the "retrograde flow from the acutely occluded left descending artery decreased markedly following occlusion of the circumflex artery. After the circumflex artery was again released, the retrograde flow increased in spite of a further fall in blood pressure. Similarly the retrograde flow from the chronically occluded circumflex artery decreased by 33 per cent following occlusion of the left descendens artery." All of these observations indicate that the collateral circulation does function following an acute coronary occlusion. It does not appear likely that the increase of retrograde flow in a matter of hours can be attributed to the formation of new collateral channels, but rather to the utilization of an already existent collateral circulation.

In view of all the evidence cited, our conception of the collateral circulation of the normal human heart may briefly be stated. There are numerous anasto-

TABLE II

| SPHERES COLLECTED FROM | DIAMETER (MICRA) | ANASTOMOSIS |
|---|---|---|
| Right coronary artery | 70 to 180 | Arterio-arterial |
| Coronary sinus | 70 to 170 | Arteriovenous |
| Right ventricular cavity | 70 to 200 | Arterio-luminal vessels<br>Arterio-sinusoidal vessels<br>Thebesian veins |
| Left ventricular cavity | 80 to 220 | |

motic channels of various types in the normal heart as has been demonstrated by anatomic studies. These have been diagrammatically summarized in Fig. 12. A summary of the diameters of the various collateral channels in the normal human heart as determined by these experiments is shown in Table II. We wish to emphasize the existence of arteriovenous anastomoses which have received little attention in the past and which deserve further study. All anastomotic channels are ready to function immediately when the need arises. The collateral circulation of the heart is not as adequate as the collateral circulation of such vessels as the femoral or carotid arteries following acute occlusion.[28] The degree of collateral circulation in the heart is not sufficient to prevent an infarct following obstruction of a major coronary artery but may limit the size of the infarction. Following acute coronary occlusion the intracardiac collateral circulation functions but in a limited way. With the passage of time, the available anastomoses enlarge.

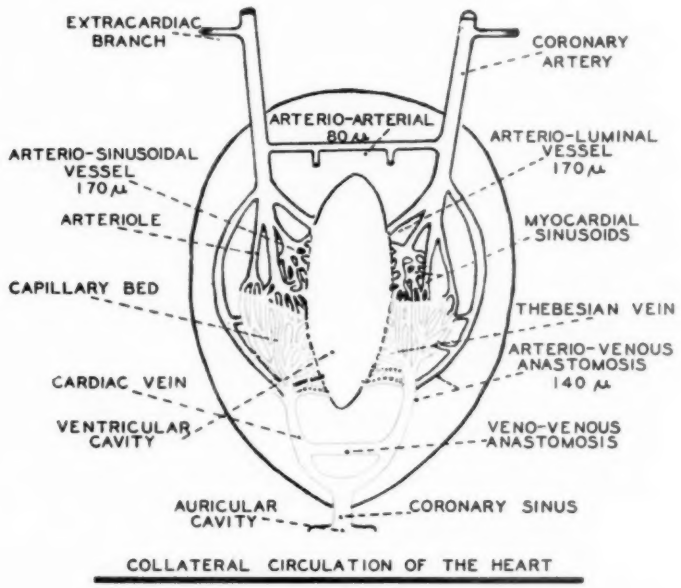



Fig. 12.—Diagrammatic representation of the collateral circulation of the normal human heart. All of these various collateral channels have been demonstrated anatomically.

## SUMMARY AND CONCLUSIONS

1. Two new methods for the study of the collateral circulation of the post-mortem human heart have been presented in order to gain further information about this circulation in the normal heart.

2. The first method utilizes a saline suspension of erythrocytes labelled with radioactive phosphorus as a perfusion medium which can be detected and measured quantitatively in any area of the heart. This method has been demonstrated to be very sensitive in that very small quantities of radioactive red cells can easily be measured. Since blood is the normal circulatory fluid, it is preferable to other nonphysiologic fluids in studies of the circulatory system.

3. After perfusion of radioactive red cells through one of the branches of the left coronary artery in normal hearts, abundant amounts of the labelled erythrocytes were found throughout the left and right ventricles. These findings indicated the existence of numerous anastomoses in the left ventricle and of a collateral circulation between the right and left ventricles in the normal post-mortem human heart.

4. The second method of study consisted of the injection of glass spheres of known size through one of the coronary arteries of the post-mortem human heart. The spheres were collected at the opposite coronary artery, the coronary sinus, and the ventricular cavities. In this way the diameters of the various anastomotic channels in the normal human heart could be quantitatively measured.

5. The largest intercoronary arterial anastomoses in the normal human heart allowed the passage of spheres ranging from 70 to 180 micra in diameter. These facts demonstrated that there are intercoronary anastomoses of arteriolar dimensions in the normal heart.

6. The existence of arteriovenous anastomoses was indicated by the recovery of glass spheres 70 to 170 micra in diameter from the coronary sinus following injection of the spheres into the left or right coronary arteries. Very little attention has been focused upon these channels in the past, and nothing is known of their functional significance in the heart. They may serve as a source of oxygenated blood to the myocardium following a coronary arterial occlusion.

7. The diameters of the anastomotic channels between the coronary arteries and either of the ventricular cavities range from 70 to 220 micra. These channels represent one or all of the following vessels: arterioluminal, arteriosinusoidal, and Thebesian veins. No apparent difference between the right and left ventricles was noted with respect to the size of these communications.

8. The normal human heart has an extensive collateral circulation with anastomotic channels of various types. When the need arises, this collateral circulation is ready to function immediately at which time the anastomotic communications may become enlarged in the presence of a favorable pressure gradient. There is evidence to show that the collateral circulation does function following an acute coronary occlusion, but only in a limited manner.

We are indebted to Drs. John L. Lawrence, Hardin Jones, L. J. Tragerman, and E. Butt for suggestions and assistance in this work.

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# INCIDENCE OF THROMBO-EMBOLIC LESIONS ACCOMPANYING MYOCARDIAL INFARCTION

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IT HAS been pointed out that death in many cases of myocardial infarction is caused by subsequent thrombus formation or by the lodgment of emboli in other organs.[1-6] If the development of thrombi could be prevented, the mortality in cases of coronary occlusion might be significantly reduced.

Recently the use of anticoagulants after myocardial infarction has focused attention on this problem. Peters, Guyther, and Brambel[4] were able to report a reduction of mortality in a group of fifty patients with myocardial infarcts treated with dicumarol. Moreover, there was only one embolus in fifty treated cases as compared with eight in a control series of sixty cases. Nichol and Page[7] have reported similar results.*

Encouraging as this is, the present methods of preventing the formation of thrombi and emboli leave much to be desired. Both heparin and dicumarol are potentially dangerous agents and may easily do more harm than good unless given under expert supervision with continuous laboratory control. The tests for and control of the activity of the anticoagulants in the body have many pitfalls for the inexperienced.[8,9] The dosage varies from patient to patient in an unpredictable manner. Hemorrhage requiring transfusion may occur,[1] and a few fatal cases have been reported.[11,12] But these agents do lessen the danger of thrombus formation. The question remains as to whether the danger of thrombosis and embolism following an infarct of the myocardium is great enough to warrant the use of anticoagulant therapy.

## MATERIAL

To evaluate the danger of thrombi and emboli following infarction of the myocardium, we have summarized reports from the literature and added statistics from an additional series of autopsied cases. Our material was taken from 2,000 consecutive autopsies performed at the Institute of Pathology, Western Reserve University, from 1935 to 1940. One hundred sixty-four cases of

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Received for publication August 6, 1946.

*Since this paper was submitted, another favorable report has appeared: Wright, I. S.: Experiences With Dicumarol (3,3′ Methylene-Bis-[4 Hydroxycoumarin]) in the Treatment of Coronary Thrombosis With Myocardial Infarction, AM. HEART J. 32:20, 1946.

recent and remote infarcts of the myocardium were encountered. The protocols of 160 of these presented sufficient data for critical analysis. There were 143 white and 17 Negro patients in the series. The ages ranged from 25 to 85 years with 72 per cent in the age group from 45 to 74 years (Fig. 1). The ratio of men to women was three to one. In Tables II, IV, and VI our results are added to those of the literature.

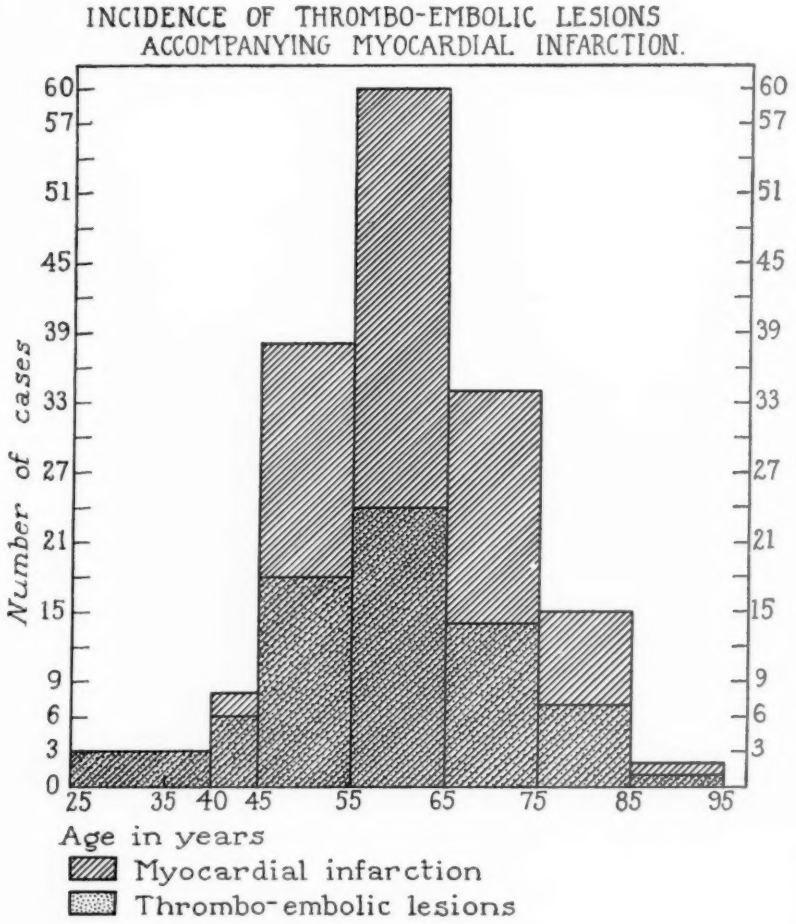


Fig. 1.

## ANALYSIS OF MATERIAL

*Incidence of Thrombo-Embolic Lesions in Myocardial Infarction.*—In 1937 Blumer[13] reported 945 cases of myocardial infarction (770 from the literature and 175 in his own series). Clinically detectable emboli or thrombi were found in 132. Since that time we have been able to add 655 cases from later reports.

The incidence of clinically detectable thrombo-embolic lesions* for the entire group is 11.5 per cent (Table I). In our autopsy series of 160 cases of myocardial infarct, 73 (45 per cent) had a total of 111 peripheral infarcts. There were 52 men and 21 women, approximately the same sex ratio as in the total series. The age incidence of thrombo-embolic lesions roughly follows that of myocardial infarction (Fig. 1). The number of cases of the younger age groups is too few for critical analysis, as over 90 per cent of the patients were more than 45 years of age. In the older groups the percentage of thrombo-embolic lesions is approximately 43 per cent.

TABLE I. PERIPHERAL INFARCTS AFTER MYOCARDIAL INFARCTION (CLINICAL CASES)

| AUTHORS | CASES WITH MYOCARDIAL INFARCTS | CASES WITH PERIPHERAL EMBOLI OR INFARCTS |
|---|---|---|
| Anderson[26] | 9 | 1 |
| Blumer[13] | 175 | 27 |
| Conner and Holt[27] | 287 | 42 |
| Gordinier[28] | 13 | 3 |
| Howard [29] | 165 | 17 |
| Hyman and Parsonnet[30] | 51 | 17 |
| Levine [31] | 145 | 17 |
| Master and associates[32] | 500 | 29 |
| Nay and Barnes [3] | 100 | 14 |
| Parkinson and Bedford[33] | 100 | 8 |
| Peters and associates[4] | 60 | 10 |
| Total | 1,605 | 185 (11.5%) |

*Etiological Factors.*—In considering the heart as a source of emboli causing peripheral infarction, we have divided our cases into two groups for analysis: (1) those with mural thrombi within the heart and (2) those without intracardiac thrombi at autopsy. It is recognized that the absence of thrombi at autopsy does not preclude the possibility of their presence and dislodgment during life.

There were sixty-five cases (41 per cent) with intracardiac mural thrombi. This agrees closely with reports in the literature (Table II). Of these, thirty-six (55 per cent) showed peripheral occlusion of vessels from either thrombi or emboli. There were ninety-five cases without intracardiac thrombi. Thirty-seven, or 39 per cent, had distal occlusion of vessels of a thrombotic or embolic nature. This last figure is important as it indicates the tendency for the occurrence of thrombo-embolic processes in organs distal to the heart in cases where the heart does not appear to serve as a source of emboli. There may be local thrombus formation secondary to altered coagulability and decreased blood flow. Also,

*In this paper the term thrombo-embolic lesions indicates infarcts of various organs due to arterial occlusion caused by thrombosis or embolism. Because the distinction between emboli and thrombi is often impossible to establish, the inclusive term thrombo-embolic lesion is used. Also included are several cases of pulmonary and cerebral embolism in which death occurred before infarction could develop.

emboli to the lung need not come from the right side of the heart, but in many instances may originate in the veins of the legs. Bean[14] found that massive emboli occluding the lumen of the pulmonary artery were always derived from the systemic veins. The leg veins were the source of massive pulmonary embolism in two of our cases. Thrombi in the right auricle were responsible in four other cases and in the twenty-seven remaining cases the origin was problematical as the leg veins were not routinely explored at autopsy.

TABLE II. INCIDENCE OF MURAL THROMBI AFTER ACUTE MYOCARDIAL INFARCTION PROVED BY AUTOPSY

| AUTHORS | NUMBER OF AUTOPSIES | NUMBER OF CASES WITH MURAL THROMBI |
|---|---|---|
| Appelbaum and Nicolson[38] | 150 | 81 |
| Bean[14] | 300 | 142 |
| Levine and Brown[35] | 46 | 38 |
| Lisa and Ring[37] | 100 | 34 |
| Meakins and Eakin[36] | 62 | 29 |
| Parkinson and Bedford[33] | 83 | 14 |
| Wolff and White[34] | 23 | 7 |
| This series | 160 | 65 |
| Total | 924 | 410 (44.0%) |

The incidence of thrombophlebitis of the lower extremities following infarction of the myocardium is 6.1 per cent in the reports listed (Table III). It is likely that the occurrence of unrecognized phlebothrombosis is even greater. It is probable that a large percentage of the emboli to the lung come from the leg veins[15] and not from the right side of the heart.

TABLE III. THROMBOPHLEBITIS OF EXTREMITIES COMPLICATING MYOCARDIAL INFARCTION

| AUTHORS | NUMBER OF CASES | THROMBOPHLEBITIS | AUTOPSY OR CLINICAL DATA |
|---|---|---|---|
| Harrington and Wright[39] | 148 | 5 | Clinical |
| Meakins and Eakin[36] | 62 | 9 | Autopsy |
| Nay and Barnes[3] | 100 | 7 | Clinical |
| Parkinson and Bedford[33] | 83 | 3 | Autopsy |
| Total | 393 | 24 (6.1%) | |

But, regardless of the course of the emboli, there can be no doubt that decreased blood flow in the lungs is a factor of great importance in producing true pulmonary infarcts. In our series, passive hyperemia of the lungs, usually marked, was found in each case of pulmonary infarction. In four cases, massive pulmonary embolism resulted in sudden death before infarcts developed.

*Location.*—Table IV gives the location of peripheral thrombo-embolic lesions in 1,146 autopsied cases of infarction of the myocardium. Since some patients had more than one thrombus or embolus the total number given in the table is not the same as the number of patients so affected. In our series of 160

TABLE IV. THROMBO-EMBOLIC LESIONS FOLLOWING MYOCARDIAL INFARCTION (AUTOPSIED CASES)

| AUTHORS | NUMBER OF AUTOPSIES | TOTAL THROMBO-EMBOLIC LESIONS | LUNGS | BRAIN | KIDNEY | SPLEEN | EXTREMITIES | CAROTID OR AORTA | MESENTERY |
|---|---|---|---|---|---|---|---|---|---|
| Bean[14] | 300 | 116 | 43 | 15 | 29 | 17 | 8 | 1 | 3 |
| Eppinger and Kennedy[5] | 200 | — | 46 | — | — | — | — | — | — |
| Garvin[6] | 133 | 128 | 45 | 18 | 32 | 19 | 11 | 0 | 3 |
| Kugel and Lichtman[41] | 95 | — | 33 | — | — | — | — | — | — |
| Meakins and Eakin[36] | 62 | 87 | 47 | 4 | 14 | 9 | 11 | 2 | 0 |
| Parkinson and Bedford[33] | 83 | 31 | 7 | 1 | 9 | 8 | 2 | 1 | 3 |
| Saphir and associates[10] | 34 | 20 | 10 | (All others, 10) | | | | | |
| Wolff and White[34] | 19 | 11 | 0 | 2 | 6 | 2 | 0 | 0 | 1 |
| Woods and Barnes[2] | 60 | 15 | 6 | 9 | 0 | 0 | 0 | 0 | 0 |
| This series | 160 | 111 | 33 | 14 | 28 | 17 | 13 | 0 | 6 |
| Total | 1,146 | | | | | | | | |
| Per cent with lesions* | | | 23.5 | 7.7 | 14.4 | 8.8 | 5.5 | 0.5 | 1.9 |

*Percentages are calculated from the series in which complete data are available.

cases, 73 had a total of 111 peripheral thrombo-embolic lesions. That is, of 160 patients examined at postmortem with myocardial infarcts, 45 per cent had emboli or thrombi in other parts of the body. Table V shows the localization of peripheral thrombo-embolic lesions in cases with and without intracardiac thrombi.

A further division of the thirty-three cases of pulmonary thrombo-embolism is as follows: in twenty-one cases only one lobe was the seat of infarction as a

TABLE V. LOCALIZATION OF THROMBO-EMBOLIC LESIONS IN CASES WITH AND WITHOUT INTRACARDIC THROMBI

| SITE | 95 CASES WITHOUT MURAL THROMBI | 65 CASES WITH MURAL THROMBI | TOTAL |
|---|---|---|---|
| Lungs | 12 | 21 | 33 |
| Kidneys | 10 | 18 | 28 |
| Spleen | 12 | 5 | 17 |
| Extremities | 9 | 4 | 13 |
| Mesentery | 3 | 3 | 6 |
| Brain | 11 | 3 | 14 |
| Total | 57 | 54 | 111 |

result of thrombosis. The lower lobes were involved in seventeen of twenty-one cases, the right lower lobe twice as often as the left lower lobe. In eight cases more than one lobe was involved (five cases involving the right and left lower lobes, two cases the right lower and middle lobes, and one case the right middle and lower, and left lower lobes). In four cases no infarct developed because of the speed with which death followed the vascular occlusion. In an analysis of thirty-three cases of pulmonary infarction, Tiedemann[16] found the right lower lobe involved in fifteen, the right upper lobe in seven, the left lower in five, the left upper in four and the right middle in two. Bean[14] similarly noted that pulmonary infarcts were most frequent in the lower lobes.

*Severity and Significance.*—The figures of Table IV are incomplete in that the extent and severity of the peripheral thrombo-embolic lesions are not mentioned. In most instances, it was impossible to gather such complete data from the literature, but the authors listed in Table VI do show thrombo-embolic lesions of lungs as the main cause of death in 10.6 per cent of the cases studied. In eight of our cases (Table VII), death was caused directly and immediately by massive occlusion of the pulmonary artery or its main branches (main pulmonary artery in one case, right pulmonary artery three cases, left pulmonary artery one case, arteries to both lower lobes two cases, and smaller branches of all lobes one case). In thirteen additional cases pulmonary infarction was contributory to death but secondary to vascular occlusion in the heart or other organs. In twelve cases pulmonary infarction was probably of minor significance.

TABLE VI. THROMBO-EMBOLIC LESIONS OF LUNGS AS A CAUSE OF DEATH AFTER MYOCARDIAL INFARCTION

| AUTHOR | CASES STUDIED | DEATHS | DEATHS FROM THROMBO-EMBOLIC LESIONS OF LUNGS | PER CENT OF DEATHS FROM THROMBO-EMBOLIC LESIONS OF LUNGS |
|---|---|---|---|---|
| Eppinger and Kennedy[5] | 200 | 200 | 13* | 6.5 |
| Master, Dack, and Jaffe[32] | 500 | 144 | 29 | 20.0 |
| Peters, Guyther, and Brambel[4] | 60 | 13 | 6 | 46.0 |
| Woods and Barnes[2] | 128 | 60 | 6 | 10.0 |
| This series | 160 | 160 | 8 | 5.0 |
| Total | 1,048 | 577 | 62 | 10.6 |

*In an additional 35 cases, pulmonary emboli are listed as an important contributory cause of death.

In addition to the cases in which death was caused by pulmonary infarction, there were twenty-two other cases in which thrombo-emboli in other locations were the main or contributory cause of death. *Thus, in 43 of 160 cases it is certain that thrombo-embolic lesions were important as a cause of death.* This agrees closely with the observations of Eppinger and Kennedy[5] who reported thrombo-embolic lesions following coronary thrombosis as a main or contributory cause of death in 49 of 200 cases.

TABLE VII. THROMBO-EMBOLIC PHENOMENA AS CAUSE OF DEATH IN 160 CASES OF MYOCARDIAL INFARCTION

| ORGANS INVOLVED | MAIN CAUSE OF DEATH | CONTRIBUTORY CAUSE |
|---|---|---|
| Lung | 8 | 13 |
| Brain | 3 | 5 |
| Leg | 3 | 3 |
| Mesentery | 2 | |
| Leg and mesentery | 1 | |
| Lung, kidney, leg, mesentery and spleen | 1 | |
| Brain, mesentery, arm and leg | 1 | |
| Spleen, kidney and mesentery | | 1 |
| Spleen and kidney | | 2 |
| Total | 19 Cases | 24 Cases |
| Per cent total number cases | 12 | 15 |

Generally, lesions of the mesenteric vessels, lungs and brain, or a combination of involvement of these structures, had the gravest clinical prognosis. Occlusion of the mesenteric vessels occurred in six cases of myocardial infarction, and resulted in death in five cases. In several cases the presenting symptoms were those of peritonitis or intestinal obstruction. Coexistent lesions in the legs or brain complicated the clinical picture in four cases. The superior mesenteric artery was occluded in three cases, twice by emboli, and once by thrombi; the inferior mesenteric once by embolism, and once by thrombosis.

Cerebral thrombo-embolic lesions were found in fourteen cases, of which two were embolic and twelve thrombotic. They were the immediate cause of death in three cases and contributory in five others. In eleven of the fourteen cases severe arteriosclerosis of the cerebral arteries was found with milder involvement of the arteries in the remaining three cases. Obviously, this cerebral vascular disease was more important in causing cerebral infarcts than were emboli from mural thrombi of the heart. As a matter of fact, eleven of the fourteen cases of cerebral infarct were found in persons without intracardiac thrombi. When the coronary arteries are sclerotic there is usually similar disease of vessels all over the body to a lesser degree. Once the heart is the seat of an infarct and factors favoring blood coagulation are brought into play, the chances are good for secondary thrombosis to occur in other locations.

This tendency to simultaneous thrombosis applies also to the extremities. Eight cases with mural thrombosis in the heart showed occlusion of the arteries to the extremities, but, there were also five cases in which there were thrombotic lesions of the leg arteries in the absence of intracardiac thrombi. There were only four of thirteen cases in which the diagnosis of embolism could be made. Arterial occlusion of the leg vessels is a serious complication and was the chief cause of death in three cases. There is frequent coincident involvement with other vital structures—brain, mesentery, and lungs (three cases).

*Control.*—In order to test the validity of our figures we have studied the incidence of thrombo-embolic phenomena in a control group of 100 cases in the

same autopsy series. The cases were selected at random from patients of a similar age, dying from causes other than myocardial infarction. Of the 100 control cases, fifteen showed thrombi or emboli.* After coronary occlusion the incidence of peripheral infarcts increases to 45 per cent. This is statistically significant.

## DISCUSSION

The diagnosis of pulmonary infarction is clinically difficult as the diagnostic criteria usually mentioned in textbooks of medicine are rarely present. In our series, the clinical diagnosis of pulmonary embolism or infarction was made in only five of the thirty-three cases in which it was found at autopsy. In eight cases, the diagnosis of bronchopneumonia was erroneously made when pulmonary infarcts were present. In the other twenty the condition was unsuspected and no diagnosis other than myocardial infarction was made. A review of the clinical records of these cases examined at autopsy showed that often there were no signs or symptoms except those that might be ascribed to cardiac decompensation or myocardial infarction. In a few, however, the occurrence of slight chest pain, a rise in temperature, pulse, or respiratory rate might have led to the correct diagnosis. Hines[1] has reported an even lower percentage of clinical recognition. In his eighty-one cases of pulmonary infarct proved by post-mortem examination, only two were diagnosed before death. He also found similarity between the signs and symptoms of pulmonary infarction and heart failure. Hemoptysis, the best single sign, occurred in approximately 33 per cent of the cases with pulmonary infarction, while it was present in 8 per cent of those with uncomplicated cardiac failure.

We do not fully understand why there should be a greater tendency for the development of thrombi in parts distal to the heart after a myocardial infarct. Undoubtedly many factors are involved. The same undetermined elements that favor the occlusion of the coronary artery must also operate in the peripheral vessels before the cardiac infarct occurs. Many cases of myocardial infarction showed coexistent thrombosis of the extremities, mesentery, kidneys, spleen, and cerebral arteries. These lesions paralleling the development of the coronary thrombosis must have had a similar pathogenesis.

After myocardial infarction the tendency of the blood to clot is further accelerated in the following ways. There is increased viscosity of the blood with the hemoconcentration accompanying shock and congestive heart failure.[17] The blood pressure falls and there is a slowing of the venous flow concomitant with the decrease in the cardiac output. A decrease in the movement of the legs with enforced bed rest and limitation of the respiratory excursion further increases the peripheral venous stagnation. A decrease in the dilute prothrombin time has been observed following myocardial infarction.[18,9] There is some question as to whether the drugs used in treatment may not increase the clotting tendency of the blood. Digitalis[19,21] aminophylline,[22] mercupurin, salyrgan,

*In two cases, thrombi were associated with contiguous inflammation (mastoiditis and meningitis). One had rheumatic heart disease and auricular fibrillation. In one case, emboli originated from the leg veins, associated with fracture.

mercuhydrin,[23] and penicillin[23,24] have all been implicated. Recent workers, however, have found digitalis to have no effect on blood clotting as measured by prothrombin times.[25] The final answer must await further investigation.

On the basis of the data presented, it is evident that vascular thrombi and emboli are serious complications of myocardial infarction. If the intravascular clotting can be reduced, the incidence of mural thrombosis of the heart itself with resultant embolism and independent coexistent peripheral thrombosis will decrease. The many patients who now die of secondary infarcts of the lung, brain, and mesentery may recover from the primary myocardial lesion and survive for a number of years. It is our opinion, therefore, that the carefully controlled, intelligent use of anticoagulant agents after myocardial infarction deserves an extensive clinical trial.

## SUMMARY

1. The incidence and severity of thrombo-embolic lesions following myocardial infarction has been studied in 160 cases of myocardial infarction encountered in a series of 2,000 consecutive autopsies.

2. Of the 160 cases of myocardial infarction 73 (45 per cent) had a total of 111 thrombo-embolic lesions.

3. Peripheral infarcts were a main or contributory cause of death in 43 of 160 cases.

4. The use of anticoagulants is thought to be warranted when proper control is available.*

We are indebted to Drs. H. T. Karsner, H. Feil, and J. M. Hayman for their suggestions and aid in preparation of the manuscript.

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# AN EXPERIMENTAL METHOD FOR THE CLOSURE OF INTERAURICULAR SEPTAL DEFECTS IN DOGS

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THE purpose of this paper is to describe a method for the closure of interauricular defects in dogs. The procedure, which will be described, is based upon a suggestion made by Dr. J. K. Lewis of the Department of Medicine.

## METHODS

*Production of Interauricular Septal Defect.*—Using intratracheal positive pressure anesthesia, the left side of the chest of the dog was opened. The lung was packed away and the pericardium exposed. The pericardium was opened and the left auricular appendage was brought into the wound. Two straight clamps were placed on the edge of the auricular appendage in such a fashion that a V was formed. The auricle was opened between the legs of the V. Opening the auricle in this way facilitated the control of hemorrhage. A curved clamp was then inserted into the left auricle until the septum was felt. The clamp was forced through the septum, opened, and then withdrawn. A silk tie was placed around the base of the two clamps which were then removed from the auricular appendage.

By this method a defect was produced in the septum which varied from 4 to 6 mm. in diameter. The resulting defect was invariably circular. The dogs were in no way disturbed by this procedure.

*Closure of the Septal Defect.*—After a period of two weeks had elapsed, repair of the septal defect was undertaken. With the dog under positive pressure intratracheal anesthesia, the right side of the chest was opened and the right auricle identified after the pericardium had been incised. By gently pushing the right auricle toward the septum, with practice one can feel the defect. When the wall of the auricle is in contact with the septum, a stitch is placed through the wall of the auricle, through the septum, and out through the wall of the auricle, as shown in Fig. 1. The stitch is then pulled up and tied. If possible, a second stitch is placed close to or into the defect. At this stage of the operation the heart rate usually becomes irregular. The distorted auricular wall now partially obstructs the vena cava. Next, a wire threaded on a needle is introduced into the auricle and made to encircle completely the part of the auricle which has

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Received for publication July 11, 1946.

been attached to the septum; the two ends of the wire are made to enter and emerge from the auricle at the same point. These steps are shown in Figs. 2 and 3. After the wire is in place, a running silk stitch is placed in the auricle and made to encircle the portion of the auricle which has been attached to the septal defect. This stitch is carried up to the point where the wires emerge from inside the auricle. Tightening the running stitch brings surrounding portions

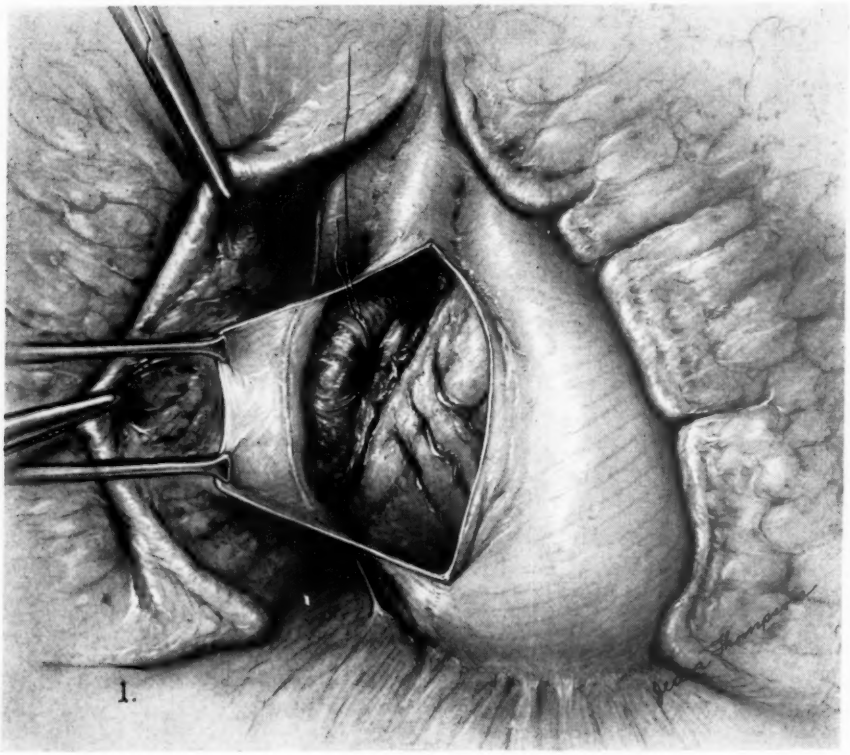


Fig. 1.—A drawing which shows the introduction of the suture from the outside of the right auricular wall which attaches a portion of the auricular wall to the septum and partially closes the defect. If possible, a second suture is similarly introduced in order to close the defect more effectively.

of the auricular wall together and buries the portion which is closing the defect, just as an appendix stump is buried. An ordinary tonsil snare is then used to pull the wires through the auricular muscle and to cut off the portion of the wall of the auricle which has been anchored to the septum. The small hole which was occupied by the snare is quickly closed by continuing the running silk stitch. The end result is shown in Figs. 5 and 6. The wire must be fairly heavy to cut through the muscular auricular wall of the dog.

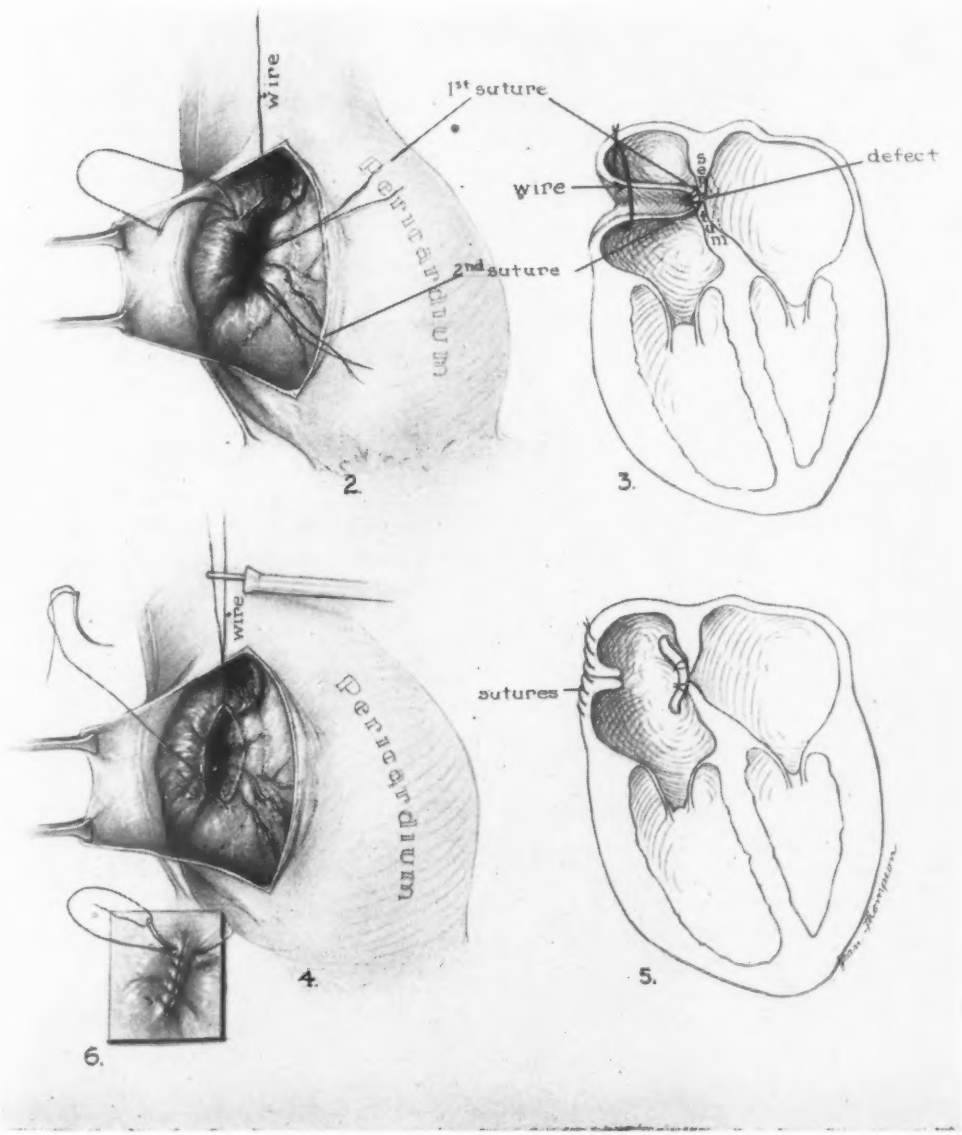


Fig. 2.—A drawing which shows the beginning of the introduction of the steel wire into the auricular muscle. The wire will be made to surround the portion of the muscle sutured to the interauricular septal defect.

Fig. 3.—A drawing showing the relation of the steel wire to the portion of the auricular wall attached to the septal defect.

Fig. 4.—A drawing which shows the completely introduced steel wire and the beginning of the introduction of the running silk suture.

Fig. 5.—A drawing showing the detached portion of the auricular wall which closes the septal defect.

Fig. 6.—A drawing showing completion of the closure of the auricular wall externally.

## RESULTS

An interauricular septal defect has been produced and closed in eight dogs. Five of the dogs survived the operation without apparent incident. Two dogs died from hemorrhage, and the heart of one dog stopped beating while it was being handled.

At the end of one month the five surviving animals were sacrificed. A collection of tissue was present on the septal wall which microscopically consisted of scar tissue and auricular muscle. A smooth scar was noted on the inside of the auricular wall at the site of the running silk stitch. In no instance were the valves of the right ventricle deformed by the procedure, but in two of the five dogs the button of tissue appeared to be large enough to impede the stream of blood from the superior vena cava. The dogs, however, appeared to be clinically well.

## DISCUSSION

In the human heart interauricular septal defects result in great dilation of the right auricle. It might be simpler to perform an operation, similar to the one described in this paper, on the large human auricle than on the small auricle of

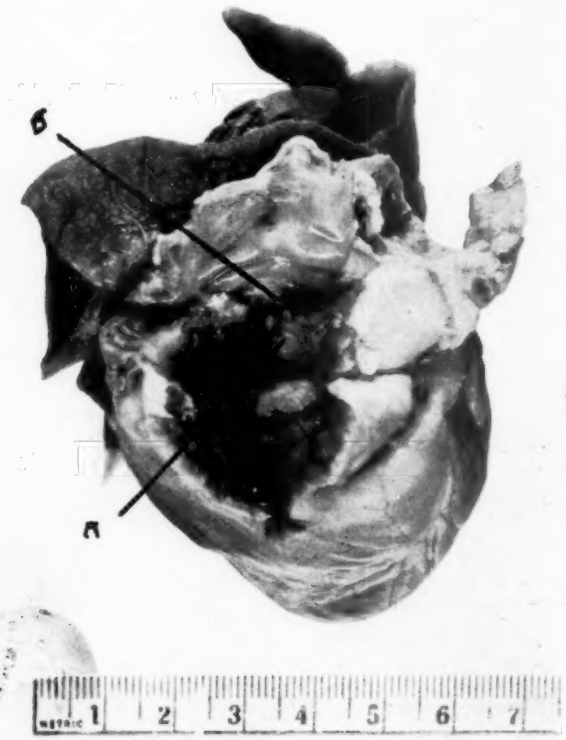


Fig. 7.—A photograph of the interior of the auricle of a dog sacrificed one month after operation *A*, A drawing which shows the size of the detached portion of the auricular wall which closes the defect. *B*, The suture line on the inner aspect of the auricular wall is also shown.

the dog. While auricular septal defects, which produce symptoms in patients, are much larger than those artificially produced in the dog,[1] it is possible that they might be closed just as easily since the human right auricle is also much larger. The dog's auricle, however, is a muscular structure and sews more easily than the human auricle.

In the dog it is apparently not necessary to anchor the attached auricular muscle completely across the defect. The trauma caused by the sutures near the defect seems to cause enough thrombus to form around the attached muscle to complete the closure of the defect.

Fig. 7 is a photograph of a dog's heart showing the size of the button of tissue found thirty days after operation, *A*, and the suture line on the inner aspect of the auricular wall, *B*.

## SUMMARY

A method is described whereby a defect in the interauricular septum in dogs can be closed.

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# TOLERANCE OF THE HUMAN HEART TO ACIDOSIS; REVERSIBLE CHANGES IN RS-T INTERVAL DURING SEVERE ACIDOSIS CAUSED BY ADMINISTRATION OF CARBON DIOXIDE

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DURING the course of a study on the effects of increased blood carbon dioxide on mental disease, severe acidosis was regularly produced in patients. In two of the patients electrocardiograms were made, and these revealed striking though transitory changes. Since intolerance of the mammalian heart to acidosis was reported several decades ago[1,2] and since a recent publication demonstrates a greater tolerance,[3] it was considered of interest to record the changes observed here.

## MATERIAL AND METHODS

Two psychotic women patients, aged 80 and 46 years, respectively, were studied. Electrocardiographic observations were made during seven experiments over a twenty-five day period on one patient and on one occasion in the other. The initial electrocardiograms in the first patient showed evidence of an old healed myocardial infarct in the CF leads but not in the limb leads.

The patients were given 15 mg. of morphine sulfate subcutaneously approximately one-half hour prior to the experiment. Curare,* 0.85 unit per pound of body weight, was given intravenously, the injection taking two minutes. Immediate disappearance of the cough and gag reflexes occurred and two or three minutes later respiration stopped. As soon as coughing and gagging became impossible and before respiration ceased, a Magill catheter was inserted into the trachea at a level estimated to be 3 or 4 cm. above the carina. A mixture of 5 per cent carbon dioxide and 95 per cent oxygen was administered at a rate of 5 to 6 liters per minute. Complete apnea lasting for ten or twenty minutes ensued, with occasional hiccoughing. During the next ten to thirty minutes the hiccoughs deepened and became convulsive gasping breaths. Efficient breathing began thirty to sixty minutes after the injection of curare. The cough and gag reflexes returned fifteen to thirty minutes later, at which time administration of the carbon dioxide-oxygen mixture was terminated. The duration of administration was forty-five to ninety minutes.

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Received for publication Aug. 7, 1946.

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When the mixture of carbon dioxide and oxygen as allowed to flow at a rate of 5 or 6 liters per minute from the tank through the catheter, the pressure in the latter was plus 2 cm. of water. When, however, the catheter was placed in the trachea the pressure was between plus 6 and plus 8 cm.; during hiccoughs it returned momentarily to atmospheric. When respiration was re-established, negative pressures were developed with each inspiration; respiration was hyperpneic and pressures as low as minus 20 cm. were recorded in inspiration.

Limb, CF, and V lead electrocardiograms were made before, during, and after administration of the mixture of carbon dioxide and oxygen. Samples of arterial blood were taken over mercury and analyzed for oxygen and carbon dioxide by the method of Van Slyke and Neill[4] slightly modified.[5] The pH was measured by means of a glass electrode.

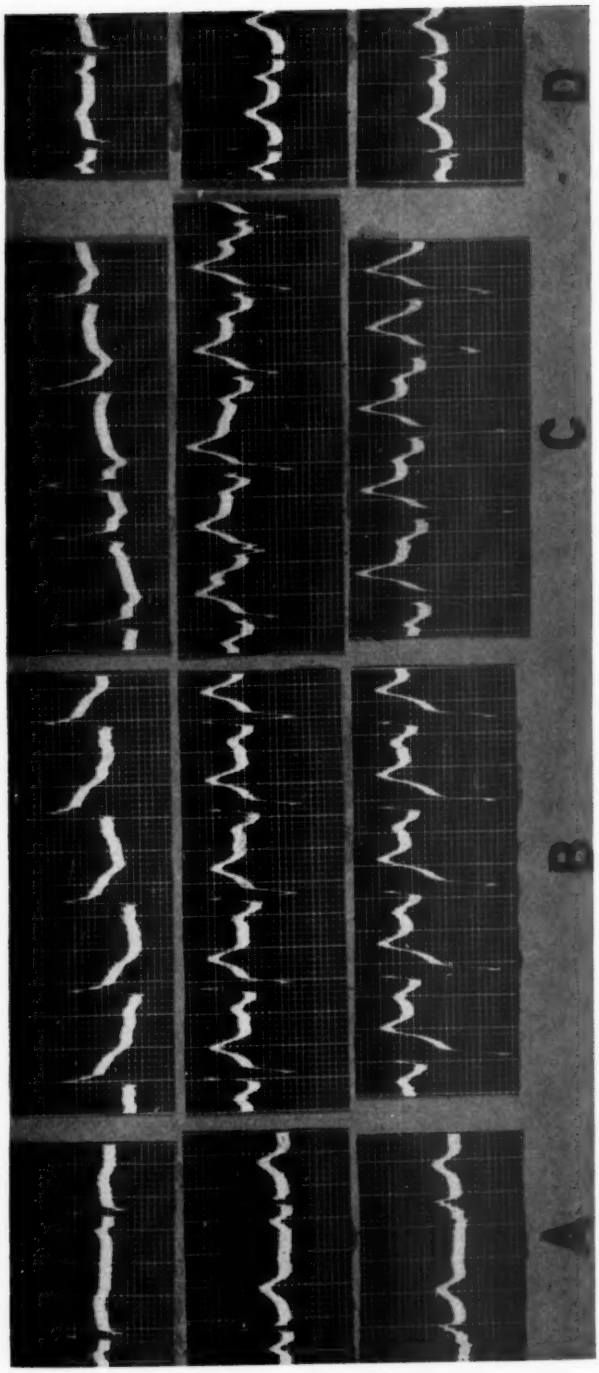
## OBSERVATIONS

The control values for arterial blood oxygen lay between 18.85 and 21.59 volumes per cent and for carbon dioxide, between 42.25 and 45.34 volumes per cent. The initial pH was between 7.40 and 7.42. During administration of the gas mixture the arterial blood oxygen was between 20.70 and 22.54 and the carbon dioxide, between 50.70 and 58.60 volumes per cent. The arterial blood pH was between 6.81 and 7.03 and averaged 6.89.

The cardiac rate was accelerated during the administration of the carbon dioxide and oxygen mixture; the P-R interval did not change appreciably. A-V nodal beats appeared. Some increase in the height of the R and T waves occurred. In one patient (Case 2) $Q_1$ became prominent. On the occasion of the first administration of the carbon dioxide-oxygen mixture in both patients, elevation of $ST_1$ and depression of $ST_3$ developed; $T_1$ or $T_3$ became inverted (Figs. 1, *B* and 2, *B*). Within thirty minutes after the cessation of administration of the carbon dioxide-oxygen mixture these changes had largely or entirely disappeared (Fig. 2, *C*). In the patient (Case 1) studied during repeated experiments, similar though less marked changes in S-T segment of the limb leads occurred during the second experiment (Fig. 1, *C*), and none at all during the third or subsequent experiments (Fig. 1, *D*). However, Leads CF and V (Fig. 1, *E* and *F*) did show changes in V waves and S-T segments at this time. This variation in the appearance of evidences in the limb leads of injury to the myocardium was not associated with lessened changes in arterial blood carbon dioxide or pH during the later experiments.

## DISCUSSION

As was recently pointed out by Gertler, Hoff, and Humm,[3] the mammalian heart is much more tolerant to acidosis than was formerly believed. These authors found no evidence of cardiac damage in dogs until the arterial blood pH fell to between 5.9 and 6.7. In the present study in man, changes in RS-T interval and inversion of T waves suggestive of a current of injury became detectable at higher pH levels, but even these were considerably lower than levels of pH encountered in acidosis in clinical practice. Gertler and co-workers[3]


A
B
C
D

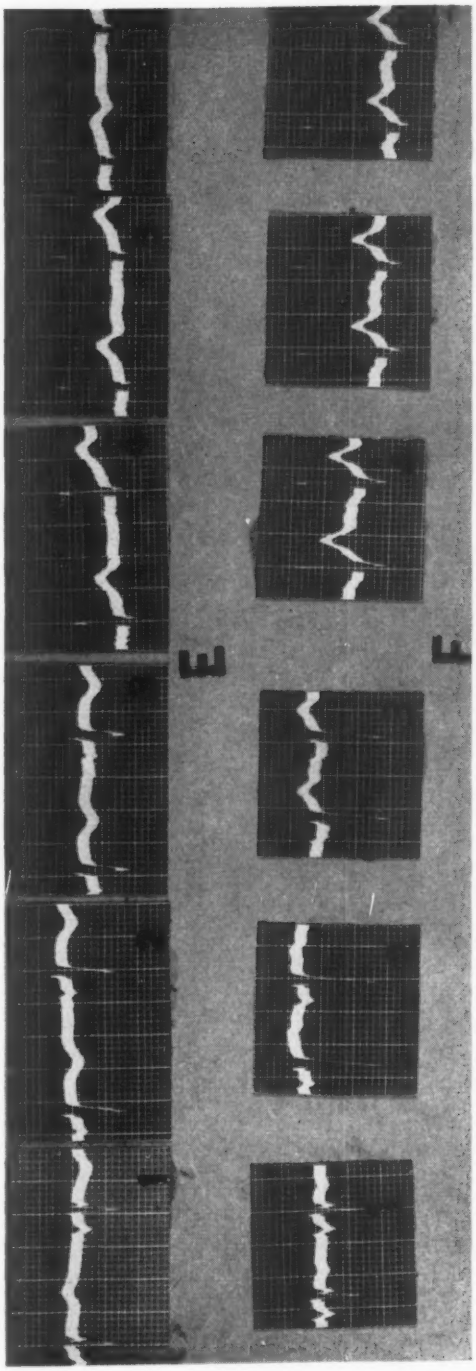



Fig. 1.—Case 1. Effect of 5 per cent carbon dioxide and 95 per cent oxygen. *A*, Control electrocardiogram; *B*, during administration of the gas mixture the first time; *C*, during administration of the gas mixture the second time; *D*, during administration of the gas mixture the third time; *E*, control V lead electrocardiogram during seventh experiment; *F*, effect on V leads of administration of the gas mixture the seventh time.

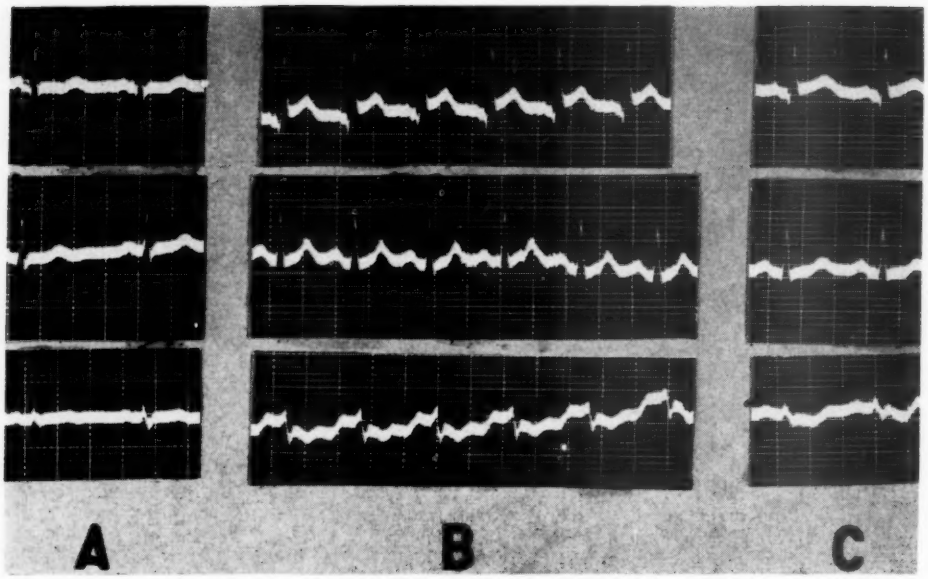



Fig. 2.—Case 2. Effect of 5 per cent carbon dioxide and 95 per cent oxygen. *A*, Control electrocardiogram: *B*, during administration of the gas mixture: *C*, twenty minutes after end of administration.

recorded only the second lead of the electrocardiogram and so may possibly have missed changes in the other leads at a higher blood pH. On the other hand, attempts made here to produce similar changes in RS-T interval and inversion of the T waves in dogs by means of a procedure similar to that practiced in the human subjects were unsuccessful.[6] It appears, therefore, that the human heart is less tolerant to acidosis than the canine.

Gertler and associates[3] concluded that the appearance of evidence of the current of injury in the acidotic dog was a terminal event, but the observations of the present study do not support this concept. Indeed, in both patients studied here it was clear that the changes were rapidly reversible after administration of carbon dioxide was discontinued, and in the one patient studied during seven consecutive experiments evidences of injury were less marked in the later ones. It is of interest in this connection that the development after a time of tolerance to carbon dioxide has also been noted in animals.[11] Clinically, all patients given carbon dioxide in the manner reported, including the two described here, remained active and well in every way; one of them, aged 80 years, subsequently was able to stand, without untoward event, the cardiac strain of a course of electrically induced convulsions given to cause remission of her psychosis. Similarly, the conclusion of Gertler and associates,[3] that the injury of acidosis is limited largely to the right ventricle, is not supported by the electrocardiograms obtained here.

As in the case of the observations of Gertler, Hoff, and Humm,[3] the present study showed no indication of the development of impaired auriculoventricular contraction during acidosis, although evidence of vagal hyperactivity in the form of A-V nodal beats did appear in the earlier experiments. The unexplained

increases in the amplitudes of the R and T waves noted by earlier workers[2,3,7,8] were also observed here.

The development of marked changes in RS-T segment in the absence of anoxia here and also apparently in the experiments of Gertler and co-workers[3] is worthy of comment in view of the fact that it has become customary in clinical practice to refer to this change as anoxic or ischemic in origin. It is to be noted that the arterial blood oxygen content was high at the time of the appearance of the abnormalities in the electrocardiogram and that other factors also operated to raise tissue oxygen tension. These additional mechanisms were increased blood flow to the tissues[9] and increased dissociation of oxyhemoglobin brought about by carbon dioxide acidosis. The question naturally arises as to whether the high concentration of oxygen administered in the present experiments might have given rise to generalized vasoconstriction, thereby producing ischemic changes in the tissues.[10] There is no evidence that such generalized vasoconstriction does occur in the presence of increased oxygen tensions, and, moreover, even small increases in carbon dioxide tension are sufficient to obliterate any tendency to localized vasoconstriction that might occur.[10]

## SUMMARY AND CONCLUSIONS

Intratracheal administration in man of a mixture of 5 per cent carbon dioxide and 95 per cent oxygen caused lowering of the arterial blood pH to the neighborhood of 6.9 and was associated with changes in electrocardiogram indicative of myocardial injury. These changes were rapidly reversible after cessation of each experiment and decreased in severity when experiments were repeated several times in the same patient. The human myocardium, though more tolerant to acidosis than was formerly believed, appears, however, to be less tolerant than the canine heart.

Electrocardiographic changes considered to be consequent to anoxia or ischemia may occur when arterial blood oxygen content is high and other factors, also making for increased tissue oxygen tensions, exist.

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# THE INFLUENCE OF HEART SIZE ON THE CIRCULATION TIME

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FOLLOWING the reports of Blumgart,[1] considerable attention has been given to measurement of the volocity of blood flow, and many methods have been introduced for the estimation of the circulation time. Most of the reports include the description of a method and its application to patients with compensated and decompensated heart disease and to patients with various conditions which influence blood velocity such as hyperthyroidism, hypothyroidism, polycythemia, and anemia.

The most consistent abnormality noted is a prolongation of the circulation time in decompensated heart disease. It is generally stated that in compensated heart disease the velocity of blood flow is within normal limits, and it is suggested that the circulation time may be utilized as an index of the presence and degree of heart failure. A review of the circulatory measurements in various reports indicates, however, that complete consistency does not exist between the circulation time and the presence or degree of cardiac decompensation.

Blumgart found a prolonged circulation time in some individuals with hypertension who showed no evidence of congestive failure. This was explained as the result of a back pressure effect on the pulmonary vessels by the hypertension. As evidence supporting this theory, experiments were cited in which compression of the aorta caused dilatation of the alveolar capillaries of the lungs with resulting slowing of the circulation. Robb and Weiss[2] state that "a correlation of the results of circulatory measurements with the degree of disability of the patients failed to reveal a strict relationship." These observers found a normal circulation time in some cardiac patients in whom clinical, x-ray, and vital capacity findings were characteristic of stasis in the pulmonary circulation. They postulated that the dyspnea and reduced vital capacity were caused primarily by an increased pressure in the pulmonary vascular bed and that this pulmonary hypertension prevented a slowing of the blood flow. Baer and Slipakoff,[3] using calcium gluconate, found that approximately 30 per cent of cardiac patients with prolonged circulation times did not have obvious heart failure. They concluded

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This study was carried out with the support of the Dorothy H. and Lewis Rosenstiel Foundation.
Read before the Annual Meeting of the American Heart Association, Inc., San Francisco, Calif., June 29, 1946.
Received for publication Aug. 5, 1946.

that in certain cases an abnormal circulation time predicted the onset of cardiac failure. Wall,[4] also using calcium gluconate, observed that all patients with congestive failure showed circulation times in excess of 20 seconds. He noted, however, that there were circulation times longer than 20 seconds in cardiac patients who presented no evidence of heart failure. Using magnesium sulfate, Neurath[5] found circulation times of 11 to 17 seconds in normal persons, 12 to 26 seconds in patients with hypertension without decompensation, and 13 to 58 seconds in patients with hypertension with cardiac decompensation. Hussey, Wallace, and Sullivan,[6] in a study of 100 cardiac patients, found fifteen in whom the circulation time was prolonged in the absence of any manifestations of heart failure. They discussed errors in technique in carrying out the procedure as a possible explanation.

It is apparent that there is not a uniformly consistent relationship between the clinical condition of the cardiac patient and the circulation time. The discrepancy observed most frequently is the presence of a prolonged circulation in individuals who show no evidence of heart failure. It is clear also that there is no general agreement as to the explanation of this discrepancy.

Several years ago a study was made of a patient with extreme cardiac enlargement secondary to chronic rheumatic valvular disease. Although this patient showed no definite evidence of cardiac decompensation, markedly prolonged circulation times were obtained by several methods. The study of this patient suggested that cardiac dilatation per se has an important influence on the circulation time.*

The patient, a 4 -year-old woman, has been under observation for about fifteen years. There was a history of rheumatic fever at the age of 12 and again at the age of 18 years. At the age of 15 years, she was told that her heart was affected and her activities were moderately restricted. When first seen there was a blowing systolic murmur and a late diastolic murmur at the apex. There was a marked generalized dilatation of the heart and an extreme dilatation of the left auricle as seen fluoroscopically in the right lateral position. At no time has there been any evidence of decompensation. She has carried on moderate social activities, has supervised her home, and, for a time, participated in a business venture with an associate. In the past ten years auricular fibrillation has been present and the ventricular rate has been controlled by small maintenance doses of digitalis, 0.5 cat unit a day. In the past year there have been periods of dysphagia apparently due to pressure on the esophagus by the dilated left auricle. On examination, there was no dyspnea, orthopnea, or cyanosis. The heart was markedly enlarged to the right and left. The heart rate was 68, the rhythm was totally irregular, and there was a blowing systolic murmur at the apex. The blood pressure was 114 systolic and 80 diastolic.

There was no evidence of passive congestion of the lungs, and the liver was not palpable. There was no peripheral edema. On fluoroscopic examination the heart shadow practically filled the chest. In the right lateral position the left auricle extended posteriorly far beyond the spine. The barium-filled esophagus was compressed and displaced posteriorly beyond the spine (Fig. 1).

On one occasion the venous pressure was 86 mm. $H_2O$, the ether circulation time was 7 seconds, and the saccharine time, 1 minute, 12 seconds. About a month later the ether time was 9.5 seconds; after the injection of saccharine a slight sweet taste was noted after 2 minutes, 7 seconds. The circulation was then studied by the use of fluorescein, which is an objective method.[7] A histamine wheal was first applied to the left forearm. After the injection of 2 c.c. of 20 per cent

*This study was reported before the California Heart Association by one of the authors (M. H. N.) May 6, 1944, under the title, "Factors Influencing Circulation Time."

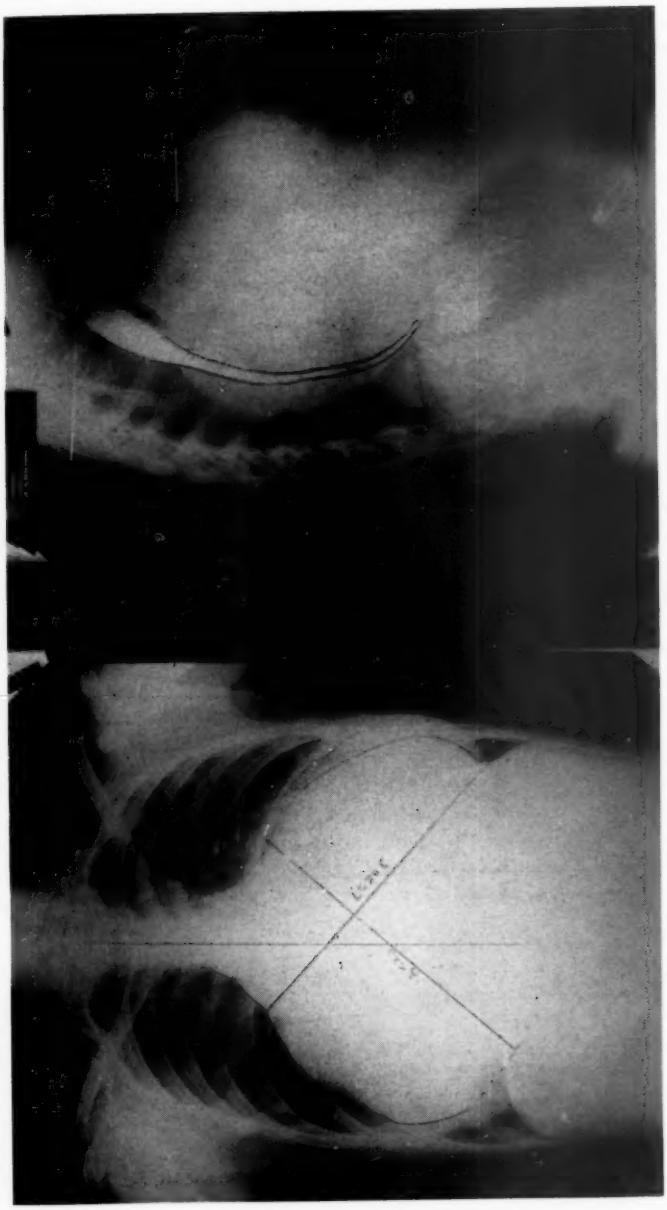

Fig. 1.—Patient R. R. Teleroentgenogram and right lateral view with barium-filled esophagus showing marked dilatation of the left auricle.

sodium fluorescein, the first appearance of fluorescence in the conjunctivae occurred at 62 seconds and in the wheal on the forearm at 64 seconds. The normal arm-to-conjunctiva time by this method is 12 to 15 seconds. Following these studies the patient has been under observation for two years and there has been no change in her clinical condition.

This patient illustrates a striking discrepancy between the circulation time and the functional state of the heart. A markedly prolonged circulation time is present in the absence of symptoms and signs of congestive failure. The cardiac enlargement is due chiefly to an extreme dilatation of the left auricle. The average normal content of the left auricle is 140 cubic centimeters. It is known that a volume of 2 liters or more may be present in cases of massive left auricular dilatation. Since the ether time is practically normal, there is no delay in the passage of the test substance from the arm vein through the right heart to the pulmonary capillaries. The prolongation of the circulation time is clearly in the circuit from the lungs to the end point. The most probable explanation is that the test substance, upon leaving the lungs, arrives at a large stagnant pool, the dilated left auricle. Here the material is greatly diluted and, presumably, poorly mixed. The blood ejected from the left ventricle contains the test substance in a highly diluted state. The prolonged circulation time may be explained by the long period necessary for the accumulation in the receptor organ of a sufficient concentration of the test substance to produce a detectable end point.

Several years ago Nylin,[8] in a study of the residual blood of the heart, reported three patients with dilated hearts in whom the circulation time was prolonged. He suggested that the increased residual blood in the heart was the basis for the prolonged circulation time. Meneely and Kaltreider[9] studied the blood volume, vital capacity of the lungs, venous pressure, circulation time, and other measurements in fifteen cardiac patients with congestive failure. They found no simple correlation between these various measurements. In eight patients, however, they noted a linear relationship between the logarithm of the circulation time and heart size as expressed by the ratio of the transverse cardiac diameter to the diameter of the chest. Aside from these references, apparently no consideration has been given to the possible role of cardiac enlargement in the prolongation of the circulation time.

## METHODS AND MATERIAL

The purpose of the present study was to determine the influence of heart size on the circulation time in compensated cardiac patients. The group consisted of ambulant cardiac patients who required only slight or moderate restriction of physical activity. Using the classification suggested by the American Heart Association, most of the patients belonged either in Class I or Class II. Since the purpose of this study was to determine the influence of heart size on circulation time, the group consisted of patients showing varying degrees of cardiac enlargement. In addition to the routine physical examination, a teleroentgenogram was made in each instance. The vital capacity of the lungs was measured in many of the patients. The circulation time was determined in most cases by the use of a solution described by Spier, Wright, and Saylor,[10]

which consists primarily of magnesium sulfate and calcium gluconate and is known as "macasol."* When injected in the arm vein, the arrival of the test substance in the throat is indicated by the abrupt development of a distinct sensation of warmth. The sensation then spreads to the hands, perineum, and lower extremities. In some instances the circulation time was checked also by the use of calcium gluconate or fluorescein. The average normal circulation time from arm to throat, using macasol, is 13.8 seconds. Variations within 25 per cent of the average value may be considered normal. For the estimation of heart size, the area of the frontal cardiac silhouette in the teleroentgenogram was utilized. This area was calculated by means of the formula $\pi/4$ long $\times$ broad diameters.[11] According to Ungerleider and Gubner,[11] this method gives values which correspond closely to the area as obtained by planimetry. The calculation is simplified by the use of the nomograms of Ungerleider and Gubner. These nomograms give the predicted cardiac area from height and weight of the patient and the actual area as calculated from the long and broad diameters of the heart. The degree of cardiac enlargement was expressed by the ratio of the actual cardiac area to the predicted normal area.

It is realized that it would be more appropriate to estimate the size of the heart by the measurement of the cardiac volume rather than the cardiac area. We have utilized the area of the frontal silhouette for the following reasons: (1) there are technical difficulties in the measurement of the cardiac volume; (2) there is a reasonably close relationship between the area of the cardiac silhouette and the cardiac volume; and (3) the measurement of the frontal projection in the teleroentgenogram is the usual clinical method for the estimation of heart size.

## RESULTS

The study includes seventy compensated cardiac patients with various types of cardiac pathology. The shortest circulation time was 9.4 seconds and the longest 62 seconds. Thirty-nine, or more than 50 per cent of the patients, had a circulation time of 20 seconds or more. The data are summarized in Tables I, II, and III, and in Fig. 2. Table II shows that there is a relationship between the

TABLE I. CIRCULATION TIMES IN SEVENTY COMPENSATED CARDIAC PATIENTS

| CIRCULATION TIME (SECONDS) | NUMBER OF CASES |
|---|---|
| 0 to 10 | 2 |
| 10 to 20 | 29 |
| 20 to 30 | 25 |
| 30 to 40 | 8 |
| 40 to 50 | 4 |
| 50 to 62 | 2 |

*Macasol contains 42 Gm. of magnesium sulfate, 16 Gm. of calcium gluconate, 0.9 Gm. of sodium chloride, and 1.0 mg. of copper sulfate in each 100 c.c. of distilled water.

TABLE II. HEART SIZE AND CIRCULATION TIMES IN SEVENTY COMPENSATED CARDIAC PATIENTS

| HEART SIZE: ACTUAL AREA / PREDICTED AREA | NUMBER OF CASES | CIRCULATION TIME (SECONDS) | |
|---|---|---|---|
| | | RANGE | AVERAGE |
| 1.0 to 1.5 | 24 | 9.5 to 41 | 19.4 |
| 1.5 to 2.0 | 33 | 10.3 to 50 | 22.8 |
| 2.0 to 2.5 | 10 | 13.9 to 41 | 26.9 |
| 2.5 to 3.0 | 3 | 15.0 to 62 | 34.3 |

degree of cardiac enlargement and the circulation time. There is a definite prolongation of the circulation time as the size of the heart increases. The data on heart size and circulation time are plotted on the graph in Fig. 2. The various types of cardiac pathology also are designated. The graph shows a considerable scatter in the values, but a statistically significant correlation between heart size and circulation time is demonstrated. The graph also reveals a tendency for the circulation times to be longer in mitral disease as compared with aortic insufficiency and hypertensive arteriosclerotic heart disease. This is further demonstrated in Table III, which shows that the mean circulation time in mitral disease is distinctly longer than in aortic insufficiency and hypertensive arteriosclerotic heart disease.

TABLE III. INFLUENCE OF TYPE OF CARDIAC LESION ON THE RELATIONSHIP BETWEEN HEART SIZE AND CIRCULATION TIME

| LESION | NUMBER OF CASES | HEART SIZE: ACTUAL AREA / PREDICTED AREA | | | CIRCULATION TIME (SECONDS) | | | |
|---|---|---|---|---|---|---|---|---|
| | | MEAN | S. D.* | S. E.† | MEAN | S. D. | S. E. | "P" VALUE‡ |
| Mitral | 22 | 1.73 | 0.50 | 0.11 | 26.9 | 11.5 | 2.5 | |
| Aoric | 15 | 1.72 | 0.33 | 0.10 | 20.2 | 8.4 | 2.2 | $> 0.05$ |
| Mitral and aortic | 11 | 1.73 | 0.22 | 0.07 | 24.8 | 12.9 | 3.9 | $> 0.6$ |
| Hypertension and arteriosclerosis | 22 | 1.60 | 0.30 | 0.07 | 19.4 | 7.9 | 1.7 | $< 0.02$ |

*Standard deviation of a single observation $= \sqrt{\frac{\Sigma d^2}{N-1}}$.

†Standard error of the mean $= \frac{S.D.}{\sqrt{N}}$.

‡Calculated according to Fisher, R. A.: Statistical Methods for Research Workers, Edinburgh, 1938, Oliver & Boyd, Ltd. The circulation time of the mitral lesion is compared with the other legions. A "P" value of less than 0.05 indicates a significant difference between the means.

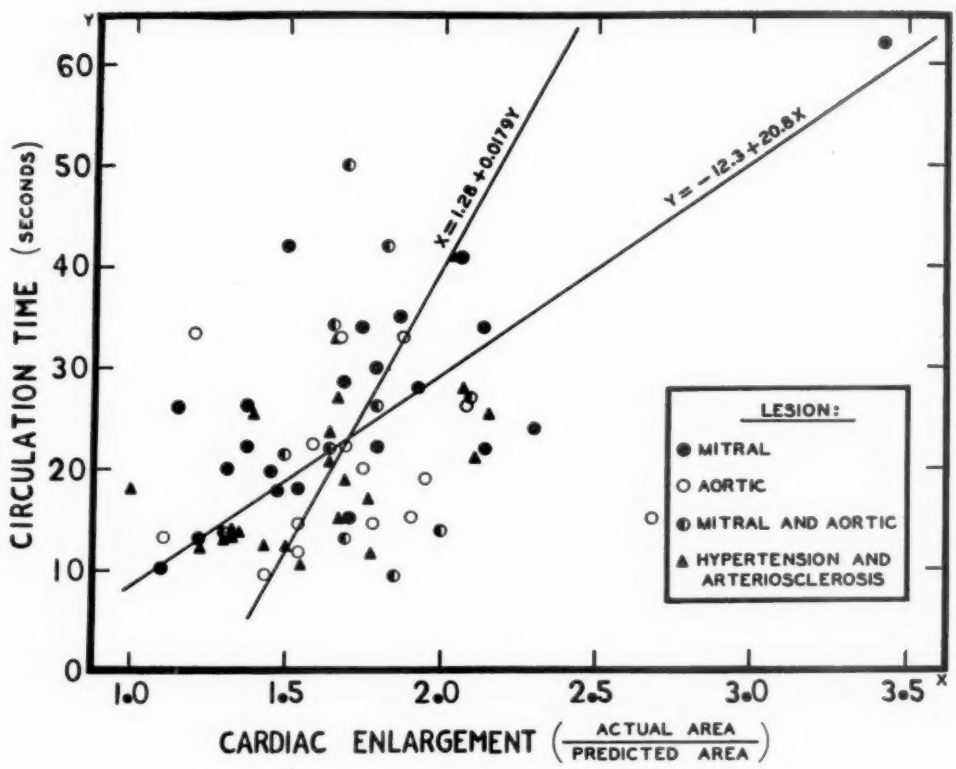


Fig. 2.—Graph showing the relationship between the heart size and circulation time in seventy patients with various types of cardiac pathology. In this graph the variables, cardiac enlargement ratio ($X$) and the circulation time ($Y$) were plotted and compared. Because the values seem to be widely scattered, regression lines were constructed, using each variable in turn as the independent and the dependent variable. The relationship between these variables was described and measured by least squares straight lines as follows: $Y = -12.3 + 20.8X$ and $X = 1.28 + 0.0179Y$. The scatter or standard error of the estimate of these lines was 8.64 seconds and 0.253 cardiac enlargement ratio. About 68 per cent of the circulation time values were in a normal distribution of $\pm$ 8.64 seconds. The coefficient of correlation was 0.610, and from this a "P" value of less than 0.001 was calculated. A "P" value of 0.001 indicates that the probability of a chance relationship between the two variables is only 1 in 1000. It follows that as the cardiac enlargement ratio increases, an increase occurs also in the circulation time.

## The following are illustrative cases:

CASE 1.—T. A., a 37-year-old man, showed the characteristic signs of mitral stenosis. He was able to carry on his work as a radio engineer with slight limitation of activity. The lungs were clear; there was no enlargement of the liver. The vital capacity of the lungs was 3,600 c.c., which is within normal limits. The circulation time was 41 seconds. Fluoroscopic examination of the chest showed a markedly enlarged heart of mitral contour. In the right lateral position the barium-filled esophagus was compressed and displaced posteriorly beyond the anterior margin of the spine. The teleroentgenogram and right lateral view are shown in Fig. 3. The ratio of the area of the frontal silhouette to the predicted area was 2.05. This is an illustration of a markedly prolonged circulation time in a patient with mitral stenosis. This case should be compared with Case 2 in which a fairly normal circulation time is associated with a comparable degree of cardiac enlargement in a patient with aortic insufficiency.

Fig. 3.—Patient T. A. Teleroentgenogram and right lateral view with barium-filled esophagus showing marked dilatation of the left auricle in a patient with mitral stenosis. The circulation time was 41 seconds. The cardiac enlargement ratio was 2.05.

CASE 2.—M. K., a 31-year-old man, presented the typical signs of aortic insufficiency. There was no evidence of congestive failure. The vital capacity of the lungs was 3,800 c.c., which is within normal limits. The circulation time was 19 seconds. Fluoroscopic examination of the chest showed a markedly enlarged heart of the left ventricular type. The pulsations of the left ventricle were very forceful. The barium-filled esophagus showed no evidence of left auricular dilatation. The teleroentgenogram is shown in Fig. 4. The ratio of the actual cardiac area to the predicted area was 1.95. This case illustrates a fairly normal circulation time associated with considerable enlargement of the heart in a patient with aortic insufficiency.

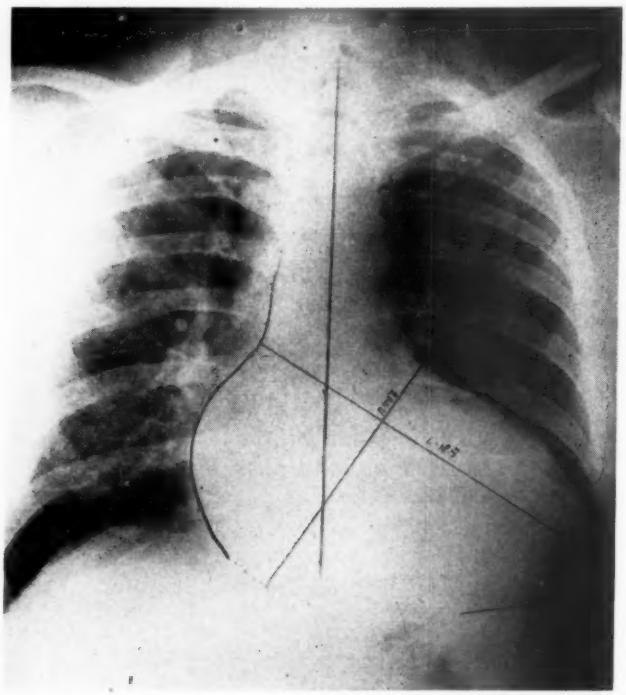

Fig. 4.—Patient M. K. Teleroentgenogram showing left ventricular dilatation in a patient with aortic regurgitation. The circulation time was 19 seconds. The cardiac enlargement ratio was 1.95.

CASE 3.—I. R., a 54-year-old man, gave a history of a coronary occlusion in January, 1945 When seen on Aug. 3, 1945, he stated that he had no complaints and that he carried on his activi ties as a business executive without discomfort. There was no objective evidence of passive congestion. The vital capacity of the lungs was 3,000 cubic centimeters. The circulation time was 27 seconds. A teleroentgenogram showed definite cardiac enlargement, the ratio of actual area to predicted area being 1.86 (Fig. 5). From January, 1946, to March, 1946, there was increasing dyspnea on moderate effort. On March 19, 1946, there were a few râles at the lung bases and the vital capacity was reduced to 2,000 cubic centimeters. The circulation time was 26.6 seconds. The findings in this patient are of interest for they indicate that in some instances the predominant factor in the prolongation of the circulation time is the cardiac dilatation and in this circumstance the development of a mild degree of cardiac decompensation may have no further appreciable effect on the circulation time.

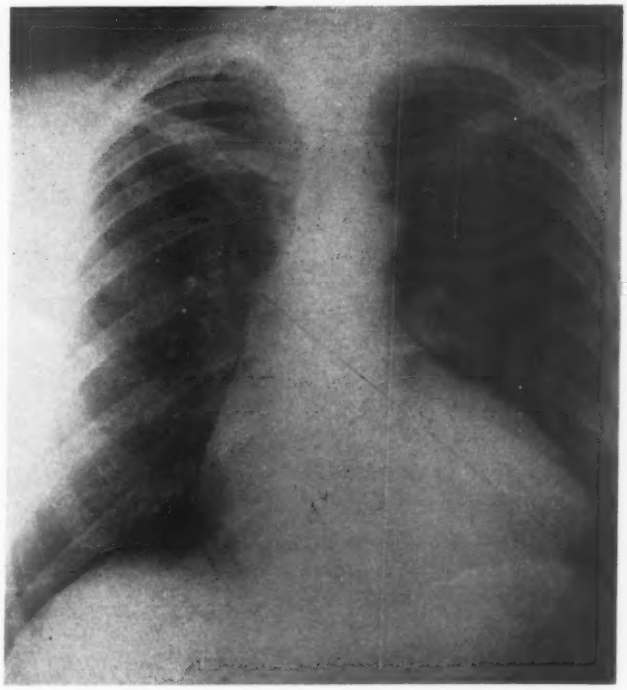

Fig. 5.—Patient I. R. Teleroentgenogram of patient with coronary disease. There was no evidence of cardiac decompensation. The circulation time was 27 seconds.

## DISCUSSION

It is evident that a prolonged circulation time occurs in patients with cardiac enlargement in the absence of symptoms and signs of congestive failure. Furthermore, there is a correlation between the magnitude of the cardiac dilatation and the increase in the circulation time. In consideration of the mechanism by which a dilated heart may influence the circulation time, it should be pointed out that the clinical measurement of circulation time includes two components: (1) the true physiologic circulation time, that is, the time required for the fastest particle of the test substance to traverse the shortest path between the point of injection and the place of detection, and (2) the time required for the accumulation in the receptor organ of a concentration of the test substance necessary for detection. These two components may be influenced in a dilated heart. The heart and blood vessels form a closed system of tubes and the velocity of flow of a liquid in such a system varies inversely as the square of the radius. Since the cross-sectional area of the flowing stream is increased, it is clear that the actual velocity of flow (the velocity of the fastest particle) is reduced in a dilated heart and that the circulation time is prolonged. Cardiac enlargement also provides conditions which delay the accumulation in the receptor organ of a detectable concentration of the test substance. The test substance entering a dilated cardiac chamber becomes abnormally diluted in the increased volume of blood. Also,

in a dilated heart, the stroke output is relatively small as compared with the large content of residual blood, and this may lead to a slow and incomplete mixing of the test substance in the intracardiac blood. Thus the blood ejected from a dilated heart chamber contains the test material in a diluted and incompletely mixed state. The level of the test substance rises slowly in the peripheral blood and there is a delay in the accumulation of a detectable concentration in the receptor organ. Nylin[12] studied the concentration in the arterial blood of intravenously injected red blood cells labeled with radioactive phosphorus. In individuals with enlarged hearts there was a delayed appearance of the labeled cells in the peripheral blood, and the rise in concentration was gradual as compared with the early appearance and abrupt rise in normal individuals.

The influence of the type of lesion on the relationship between heart size and circulation time is of interest. Two explanations for the relatively longer circulation time in mitral disease may be considered. First, the area of the frontal silhouette may give an inadequate measurement of the cardiac volume in mitral disease as compared with lesions which predominantly affect the left ventricle, such as aortic regurgitation and hypertensive heart disease. In mitral disease a considerable volume of the residual blood is in the dilated left auricle and this chamber is not at all or only partially visualized in the frontal projection. Thus the longer circulation time in the mitral heart may be consistent merely with a cardiac volume which is incompletely expressed by the area of the frontal silhouette. Second, there is the possible difference in the reaction of the test substance in the mitral heart as compared with the heart of aortic insufficiency or hypertension. The pulsations of the dilated left auricle in mitral disease are wavelike and of small amplitude. This may effect a relatively slow and incomplete mixing of the test substance in the intra-auricular blood. In aortic insufficiency and hypertension, the increased residual blood is chiefly in the left ventricle. The contractions of this chamber are active and forceful, favoring a rapid and complete mixing of the test substance. In Nylin's study[12] on the dilution curves following the injection of labeled red blood cells, there was one exceptional case in which the heart was considerably enlarged and yet the rise in the level of the tagged cells was rapid and abrupt, similar to the response in hearts of normal size. It is of interest that the diagnosis in this case was aortic regurgitation.

The demonstration of the influence of the intracardiac blood on the circulation time modifies some of the accepted interpretations of circulation time measurements. Blumgart[1] studied the circulation time from the arm to the right heart and from the right heart to the periphery. He considered that the time of flow from the right heart to the periphery was a measure of the velocity in the pulmonary circulation since most of this time is spent in the flow through the lesser circulation. He disregarded the time of flow through the heart, indicating that this interval is very short. Although this is true in the normal heart, the present studies show that a dilated heart can participate substantially in the prolongation of the "pulmonary" circulation time. It is apparent that the use of the "pulmonary circulation time" as an index of the velocity of blood flow through

the pulmonary circulation would lead to an incorrect interpretation of circulatory measurements.

It is clear that an increase in the amount of blood interposed between the site of injection of the test substance and the point of detection will prolong the circulation time. In the arm-to-head segment, the increased volume involves chiefly the intrathoracic blood which includes the content of the heart and the content of the pulmonary vessels. In cardiac disease, the increased blood volume may be limited to the heart or it may include both the heart and pulmonary vessels. The intracardiac blood content may be greatly increased without affecting the clinical condition of the patient, but an increase of the volume in the pulmonary circulation (pulmonary congestion) results in dyspnea, orthopnea, and cough. Thus the following combinations may occur: (1) a pro-

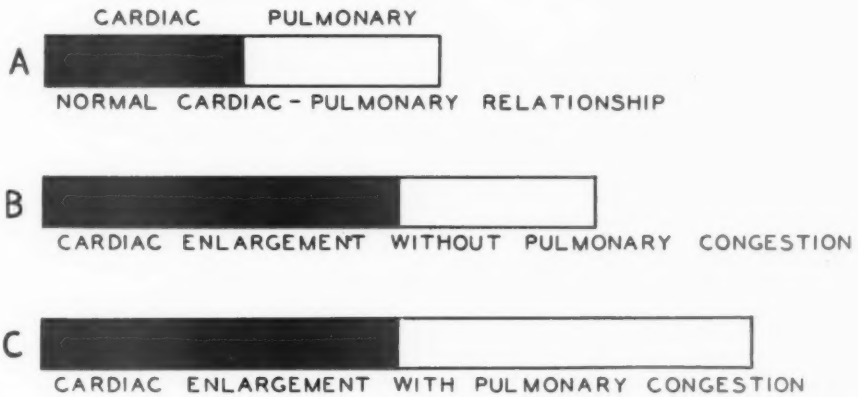


Fig. 6.—Diagram showing the influence of the distribution of the intrathoracic blood in determining the relationship between the circulation time and the clinical condition of the patient. *A*, Circulation time normal, congestive failure absent. *B*, Circulation time prolonged, congestive failure absent. *C*, Circulation time prolonged, congestive failure present.

longed circulation time with no evidence of congestive failure, in which situation the increased blood volume is limited to the heart, and (2) a prolonged circulation time associated with congestive failure, in which the increased blood volume includes both the heart and the pulmonary circulation. This is shown diagramatically in Fig. 6. In evaluating the significance of a prolonged circulation time it is evident that the influence of cardiac dilatation must be taken into account. The recognition of the cardiac factor provides a broader and more accurate interpretation of circulation time measurements.

## CONCLUSIONS

1. In seventy compensated cardiac patients with cardiac enlargement, the circulation time was longer than 20 seconds in more than 50 per cent.

2. There was a rough correlation between the degree of cardiac enlargement and the circulation time.

3. With a comparable degree of cardiac enlargement there was a relatively longer circulation time in patients with mitral disease than in patients with aortic regurgitation and hypertensive arteriosclerotic heart disease.

4. A prolonged circulation time does not necessarily signify an actual reduction in the velocity of blood flow but may be due entirely to an improper mixing and a dilution of the test substance in the increased residual blood of a dilated heart.

5. The relationship between the circulation time and the clinical condition of the patient depends on the manner of distribution of the intrathoracic blood.

## ADDENDUM

Since this paper was submitted for publication, the following report has been published by Gernandt, B., and Nylin, G.: The Relation Between Circulation Time and the Amount of the Residual Blood of the Heart, AM. HEART J. **32**:411, 1946. This report clearly demonstrates a significant correlation between the heart volume and the circulation time in both compensated and decompensated heart disease.

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# A PRELIMINARY STUDY OF THE CORONARY CIRCULATION POST MORTEM

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THE purpose of this preliminary report is to emphasize the need for a rapid, complete, and objective method of routinely studying the coronary circulation post mortem and to present a technique which meets these needs.

As to the need, Karsner[7] says, "Of the various diseases [of the heart] which are of importance, arteriosclerosis of the coronary arteries, because of the frequency in those periods of mature life when the integrity of bodily function serves in a large sense the welfare of mankind, deserves most intimate study." And yet, accumulations of accurate objective data on coronary disease are relatively scanty.

*Rapidity of Technique.*—A rapid technique is desirable so that the clinician may be presented, within a reasonable length of time (approximately one to one and one-half hours after the heart has been removed), not only the gross pathologic changes in the three layers of the myocardium and in the cardiac valves, but also a complete two-dimensional visualization of the entire coronary circulation by means of a wet roentgenogram.

*Completeness of Technique.*—The technique must offer a complete injection of the arterial system as far as precapillary arterioles. It should also lend itself readily to a systematic clinicopathologic study of diseases of the heart in general and specifically those of the coronary arteries.

*Possible Lines of Investigation.*—A complete injection technique suggests certain lines of investigation.

*Correlation of Cardiac Arrhythmias With Disturbances in Circulation*: Gross and associates[4,5] described a distinct and specific blood supply for the principal segments of the conduction system and found that morphologic disturbances of the system could be correlated with functional derangements. These significant observations require further study (Fig. 1).

*Correlation of Atrial Infarcts With Circulatory Disturbances*: Since the report of Wartman, Feil, Cushing, and Stanton[25] recognition of atrial infarcts has become more widespread, yet the etiology has remained obscure. By injection and

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Received for publication July 31, 1946.

radiographic visualization of the coronary tree, the demonstration of the presence or absence of occlusions in atrial branches, or in the parent artery proximal to their origin, may help to clarify the cause of atrial infarcts.

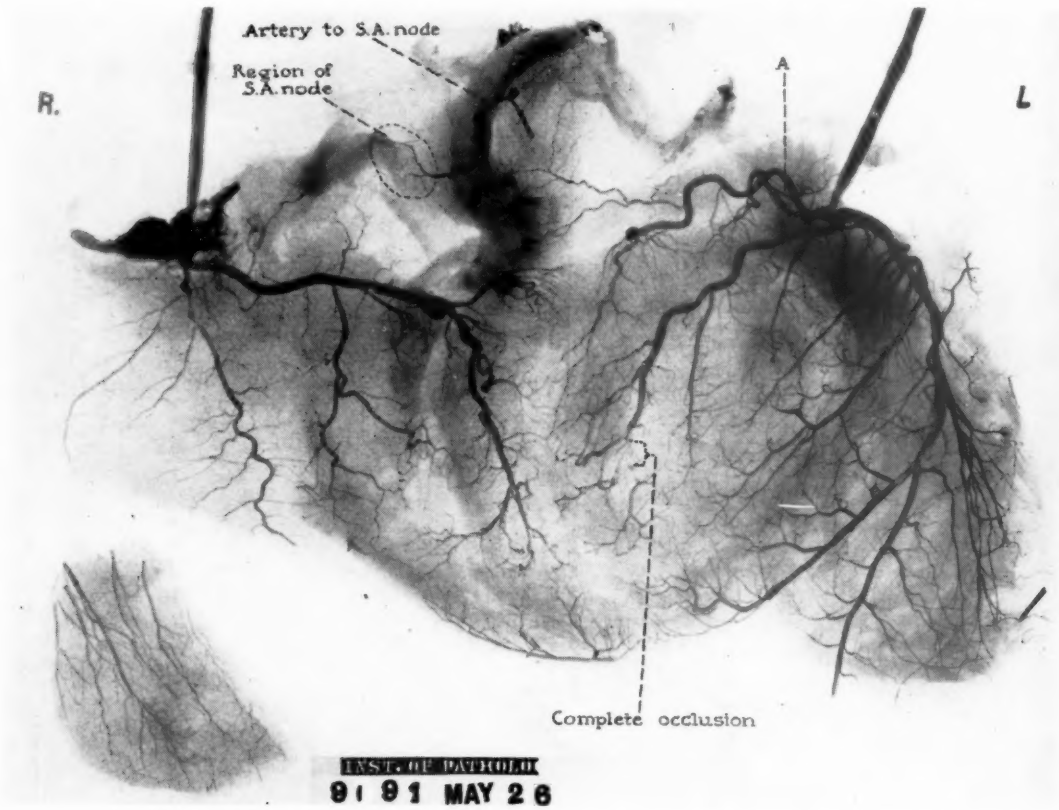


Fig. 1.—This 69-year-old white woman has had electrocardiographic changes of "left typical bundle branch block" for approximately two and one-half years. At autopsy an organizing complete occlusion was demonstrated in the distal radicals of the marginal branch of the circumflex ramus of the left coronary artery. Moderate endocardial sclerosis was diffusely demonstrable over the left ventricular portion of the interventricular septum.

*Growth of Coronary Circulation*: Some authors maintain that a pattern of growth is responsible for the relevant changes that occur in the coronary arteries, usually in middle life. Others conclude that regardless of the ontogenetic process, "the event which precipitates occlusion of a coronary artery is not referable to the history of the artery, but to an accident, morphologic, metabolic, immunological, or bacteriological."[2] A routine standardized method of visualization of the coronary arteries from infancy to old age might shed some light on these fundamental concepts.

*Genetic Aspects of Coronary Circulation*: Schlesinger[18,19] has found after, studying 269 hearts, that the coronary artery pattern is not exactly the same in any two human hearts and that these multitudinous variations can be classified into three distinct anatomic patterns, each differing in its vulnerability to arte-

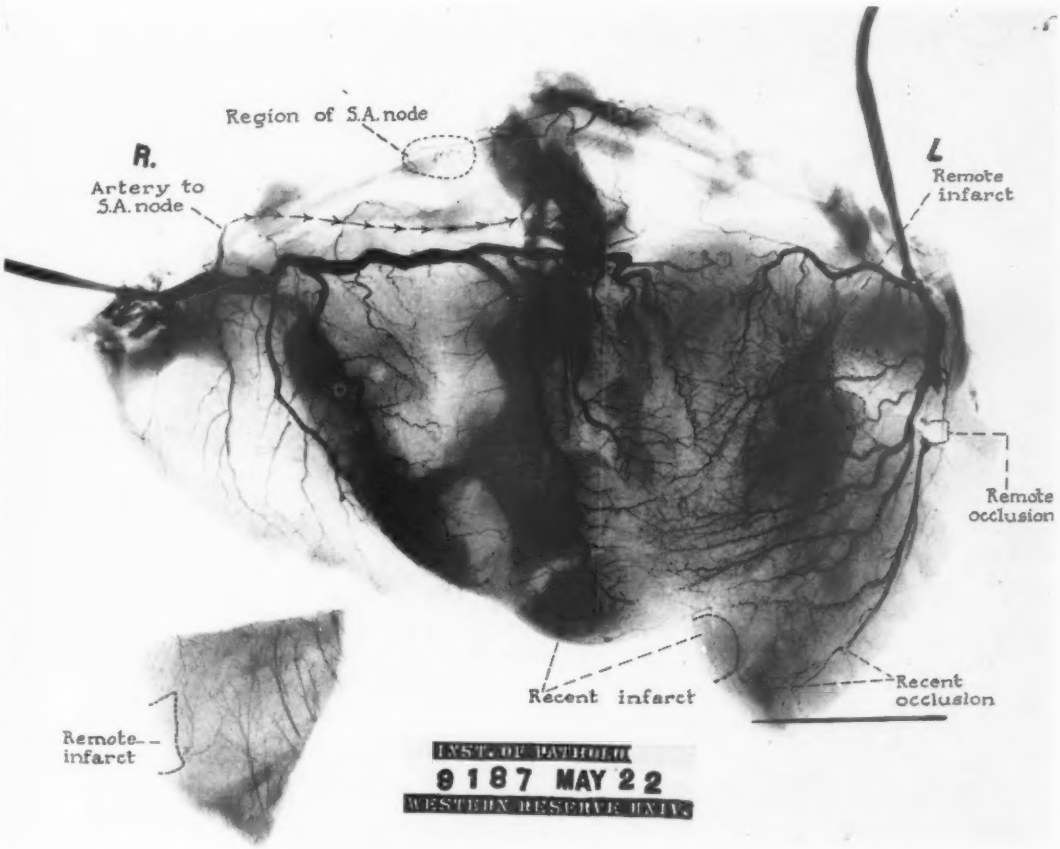


Fig. 2.—This 52-year-old white man with diabetes died from carcinoma of the right lung with metastases to the liver. Acute bacterial endocarditis of noncoronary cusp of the aortic valve was discovered at autopsy, with occlusion of a small terminal radical of the descending ramus of the left ventricle, measuring 1.4 by 1.8 by 1 centimeter. A remote occlusion of the descending ramus of the left coronary artery approximately 3 cm. from the origin and extending .7 cm. was located. An electrocardiogram taken approximately one month before death was reported as a normal record. Note this is a 2 plus right preponderant coronary artery pattern.

riosclerosis (see Fig. 2). With these observations he concludes that the well-known familial tendency to coronary artery disease may be a function of inherited patterns of the coronary arteries. He also feels that correlation of electrocardiograms with these patterns may be possible. Objective records of the coronary arterial circulation, routinely gathered from autopsies, would serve to confirm or negate these interesting speculations.

*Deep Divisions of the Coronary Arteries:* Wearn and collaborators[26-30] found, "That finer divisions of the cornary arteries present a far more complex picture [than the larger vessels] the knowledge of which is still incomplete and in some cases controversial." Whitten and Barnes,[32] after studying these finer branches, have attached significance to the angle at which, from the exterior, a coronary artery branch penetrates the substance of the cardiac muscle. The necessity of a medium which will consistently penetrate these fine channels and lend itself to corrosion with the production of nonfriable, nonbrittle, elastic casts becomes evident for a comprehensive clinicopathologic correlation of the deep circulation of the heart. It follows also that with increasing skill in the surgical treatment of coronary disease and with the ultimate death of patients so treated, the pathologist must be equipped to evaluate objectively the extent of surgically created collaterals.

**Fig. 3.—Vascularity in the posterior leaflet of the mitral valve injected with red with the medium from the left coronary artery.**

*Vascularity of Valves*: For the demonstration of vascularity in the heart valves post mortem, there is probably no substitute for the microscope.[8] However, it is certain that the routine sections may occasionally by-pass the region of vascularity. A method of directing attention to these regions, as by a colored radiopaque injection mass, is desirable for a more complete correlation of the minimal valvular lesions, so frequently seen at the autopsy table, and of the other established stigmas of rheumatic fever, such as Aschoff nodules and endocardial reduplication of valves (see Fig. 3).

*Muscle Bundle Concept of Cardiac Pathology*: Based on the earlier studies of MacCallum[10] and Mall[11] on the demonstration of distinct muscle bundles in the human heart, Robb and co-workers[12-17] have presented some novel concepts with important potentialities. These observations have not been fully confirmed, but only because there has been little investigation along these lines. A technique of complete arterial injection with the formation of a solid flexible cast would lend itself readily to further correlation of muscle bundle patterns with coronary artery patterns.

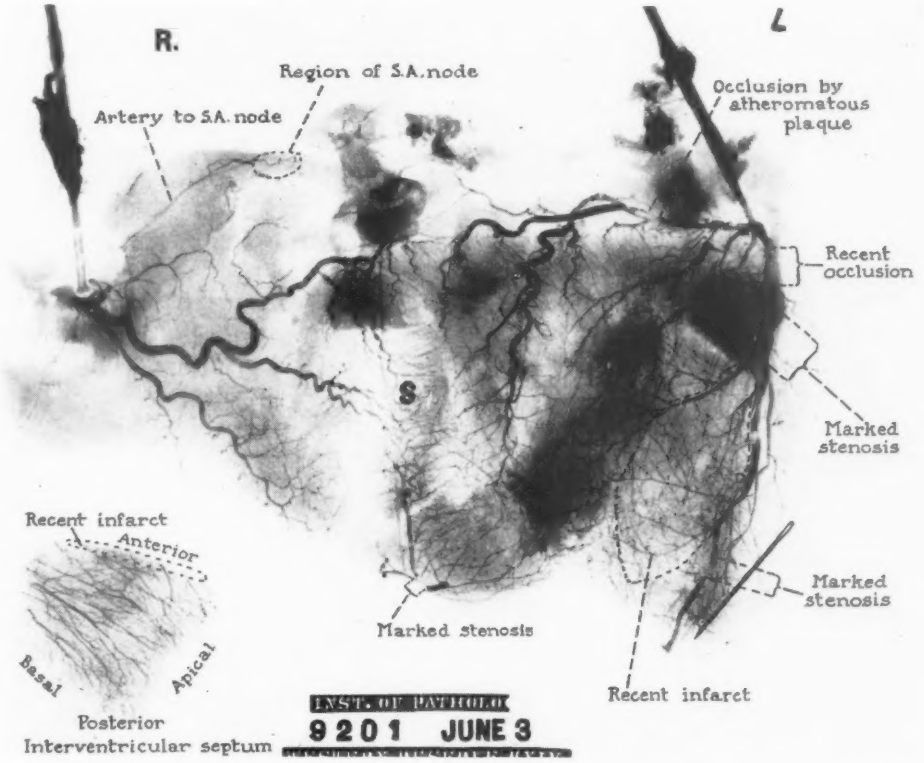


Fig. 4.—Approximately 80 per cent of the arterial system was injected with the blue medium from the right coronary artery, including most of the vessels seen within the area of recent infarct and more than 90 per cent of the interventricular septum. No established arrhythmias were noted clinically. (Note the artery to the sinoauricular node arises from the nonoccluded right coronary artery.) *S* indicates the area of enucleated septum. The patient died in heart failure approximately four days after clinical manifestations of acute myocardial infarct.

*Prognosis of Coronary Disease*: Fifty per cent of all men over fifty years of age studied by Schlesinger[19] revealed at least one occlusion somewhere in the coronary arterial system. It would seem, therefore, that any statistical data as to the incidence or prognosis of coronary disease would have to include occlusions and, as will probably follow, infarcts that have hitherto gone unrecognized by the routine manual method of dissection of the coronary tree (see Fig. 4).

*Objectiveness.*—A fundamental postulate for accurate inference from mass data is that the records which compose the data be assembled by objective standardized methods. Notoriously inadequate are descriptions of the coronary arterial system which speak of minimal and moderate sclerosis, stenosis, etc. Similarly inadequate are descriptions of infarcts as anterior or posterior, basal, or apical. The following is a description of a technique, aided by illustrations (Figs. 5 and 6), which can be routinely employed in the study of the coronary arteries post mortem, without the sacrifice of other pathologic entities, and which will lend itself readily to a study of the problems mentioned.

## HISTORICAL DATA

The literature discloses many and diverse methods for demonstration of the vascular system of the human body. All of these have been applied in one way or another to the study of the coronary arteries. The first method was simple dissection, which von Haller[24] used in 1757 to give the first detailed knowledge of the blood supply to the heart. A systematic study of this field, even today, cannot be had without the aid of dissection. Certain plans have, however, greatly facilitated this long and, of necessity, incomplete procedure.

The earliest investigators injected dyes, and in some cases silver nitrate, for the purpose of recognizing the blood vessels in both gross and microscopic preparations. Swammerdamm,[22] in 1672, was the first to inject a substance which would harden in the coarser vessels. This medium, hot wax mixed with oil and fats and stained with cinnabar, was used almost exclusively throughout the eighteenth century. Additional methods have been adequately reviewed in the classical monographs of Spalteholz,[21] Gross,[4] and Whitten.[31]

A recent significant contribution was that of Schlesinger,[19] who devised a technique of unrolling the heart, so that the entire arterial system could be laid out on one plane, strikingly resembling the Spalteholz diagram. Schlesinger's technique with the use of a lead phosphate agar mass was employed in a total of twenty-seven hearts. However, it was necessary to abandon the use of his medium for the following reasons: (1) A great deal of time was consumed in the preparation of the medium and it was found to be unstable when prepared; (2) the mass was not fine enough to penetrate the small vessels consistently; (3) it was found to be inadvisable to suspend the heart in warm saline (44°C.) for twenty minutes or longer; (4) it was not possible to prepare corrosion specimens; (5) it was not possible to prevent leakage from the small vessels adequately while injecting.

In 1937 Hill[6] suggested the use of latex rubber in various anatomic procedures. Batson,[1] Gamble,[3] and Tobin[23] have used this compound to advantage, and Lieb[9]

has developed a technique for the use of Neoprene, a synthetic latex, in adequately demonstrating the vascular bed of the human kidney. Most of her work was done with corrosion specimens, and the technique, because of the time consumed before demonstration, does not lend itself to a routine practical study of the coronary circulation. Recently, Smith and Henry[20] have used Lieb's technique in injecting the dog heart.

Neoprene, although less desirable than latex, because of its slowness of gelation in cold temperatures and its greater instability when employed with barium sulfate, may, however, be adapted to the following technique.

## TECHNIQUE

*Apparatus.*—The apparatus consists of a mercury constant pressure trap which is connected to an air pressure line. The desired constant pressure may be obtained by raising or lowering the inner tube. A Wolff bottle serves as a reservoir for this air pressure and a mercury manometer has been utilized so that the pressure in the apparatus may be accurately gauged. A liter bottle is used for the saline and the latex bottles have a capacity of 100 cubic centimeters. These bottles have been graduated so that the amount of latex which fills each coronary artery can be measured. The rubber tubing connections should be as short as possible, for it is difficult to clean all of the latex out of the tubes. If, however, the tubes are thoroughly rinsed immediately after use, they may be used again, three or four times. The vacuum jar (Fig. 5) may be obtained commercially.*

*Cannulation.*—The right and left coronary arteries are dissected free as they originate from the aorta, and two-inch glass cannulae are securely fastened into the arteries, as close to the origin of the vessels as possible, with 40-gauge cotton suture. (A bowknot facilitates the removal of the cannulae after injection has been completed.)

The cannulae are prepared from glass tubing (3/16 inch with 1/16 inch bore). The tube may be drawn out to any desired bore, and with intravenous needles varying from 18 to 25 gauge the cannulae are flanged in the following manner: the needle is coated with talcum powder and heated until the head becomes red hot. By quickly inserting the needle into the cannula and exerting pressure against the needle, the desired flange will be produced (Fig. 6). It has been found that a cannula with a short blunt head will make possible injection of vessels which arise close to the origin of the coronary arteries.

*Washing.*—After the cannulation the heart is washed with a total of approximately 500 c.c. of physiologic saline at room temperature. The washing is done separately for each coronary artery and is completed when the return flow from the opposite coronary artery is clear. Simultaneous washing of the coronary arteries was abandoned after the suggestion of Lieb,[9] that interstitial edema might occlude the smaller rami of the arterial tree and thus prevent a complete injection. The swelling of the heart was noted to be significantly less with the independent washing of each vessel.

*Sold under the name of Jumbo Vacuum Jar Number 820 by the American Thermos Bottle Co., Norwich, Conn.

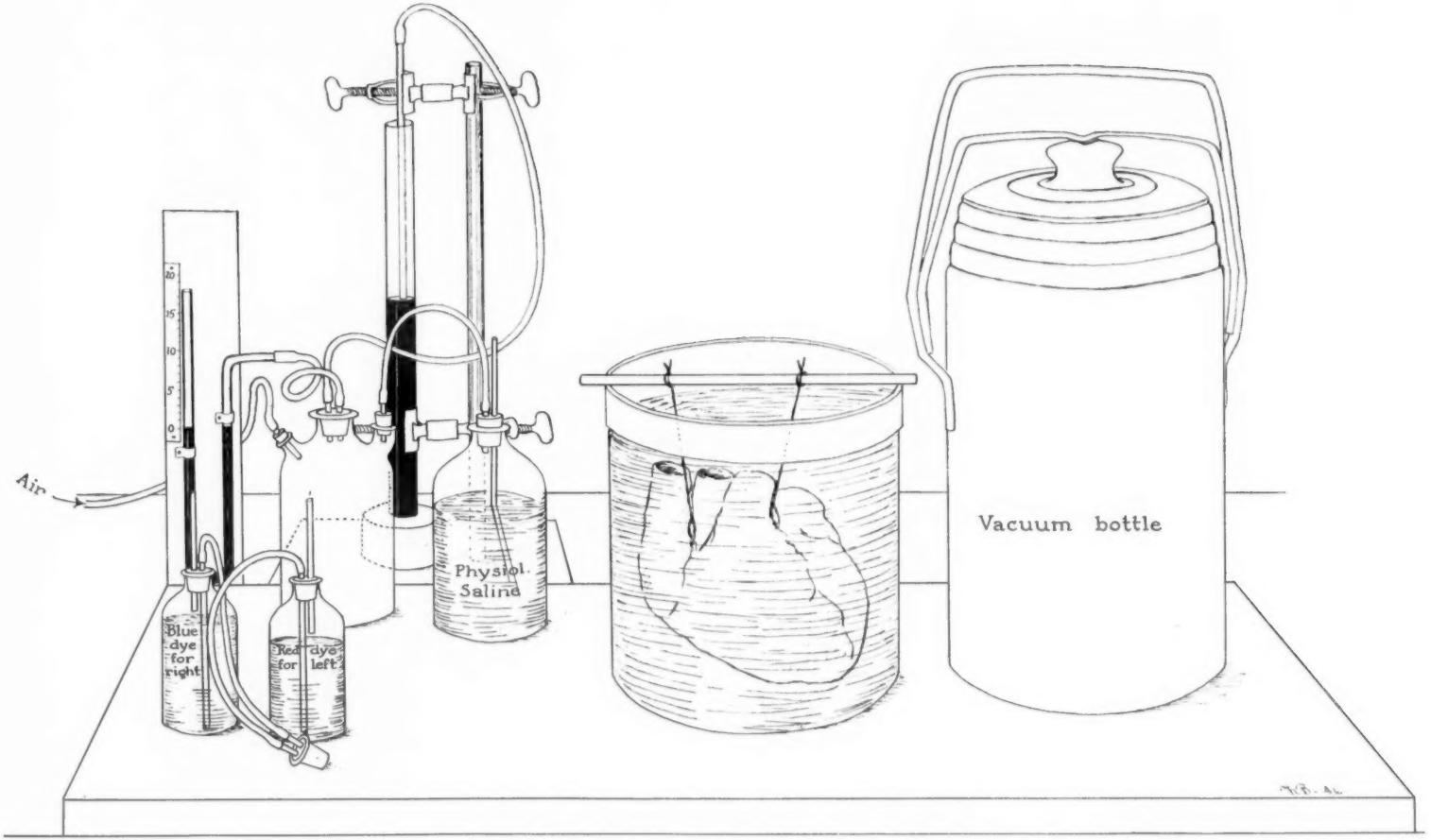


Fig. 5.—Diagram showing apparatus described in text.

*Injection.*—A suspension of barium sulfate in an aqueous ammoniated solution of latex rubber is employed.† Compound No. 60-22724 A (red) and 60-22724 B (blue) was selected because it provides maximum radiopacity with consistent injection of precapillary arterioles of 15 to 25 micra in luminal diameter. A 2 per cent aqueous solution of ammonium hydroxide may be used to dilute the compound to a viscosity approaching that of water, at the expense, however, of diminishing radiopacity. The medium is prepared with red and blue organic dyes (injected into the left and right coronary arteries respectively) which do not bleach with the subsequent treatment. When the union of red and blue material occurs, as with intercoronary anastomoses, the colors are maintained and the vessels appear streaked with red and blue.

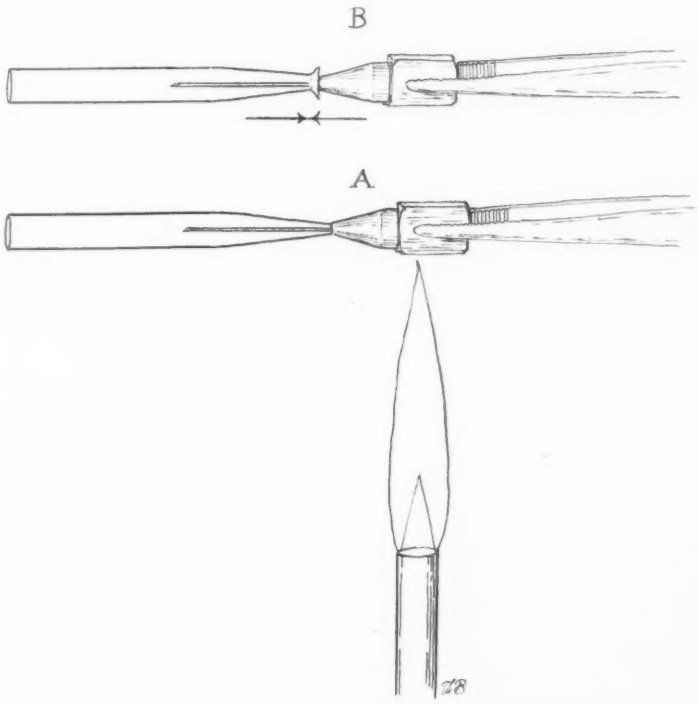


Fig. 6.—*A* illustrates the heating of the needle while inserted in the glass tubing. *B* illustrates the resulting flange when pressure is exerted with the hot needle.

Pressure is allowed to build up in the apparatus until the desired level is reached before the clamps on the tubes leading to the cannulae are released. This permits maximal pressure to be released and the vessels to be injected simultaneously. Originally an effort was made to simulate the ante-mortem pressure. Consistently good results, however, were obtained with pressures of 150 mm. Hg for adult hearts and 100 mm. for hearts weighing 150 grams and less.

The heart is suspended during injection in a solution of 2 per cent glacial acetic acid and 4 per cent formaldehyde in 70 per cent ethyl alcohol, which

†Obtained from American Anode Company, Akron, Ohio.

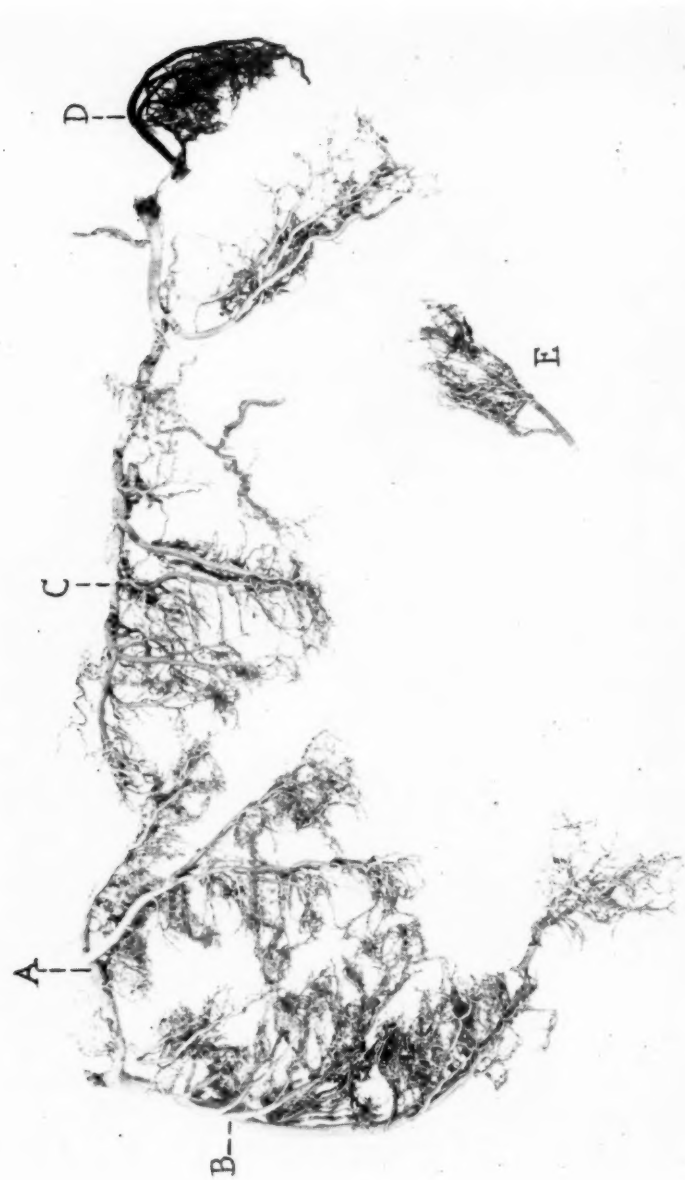


Fig. 7.—Corrosion specimen of the normal heart with injection of right accessory coronary ostium and the cast of its circulation. *D*, *A*, Circumflex ramus of the left coronary artery. *B*, Descending ramus of the left coronary artery. *C*, Main right coronary artery. *D*, Accessory right coronary artery. *E*, Interventricular septum (more than 80 per cent of the vessels injected from the left coronary artery).

promptly coagulates the compound as it escapes from the minute vessels severed in the process of removing the heart. Injection is completed in from five to fifteen minutes, depending upon the size of the heart. The pressure is maintained in the vessels after injection by means of bulldog clamps placed on the rubber tubes leading to the cannulae. The heart is then placed in a vacuum bottle containing a 95 per cent alcoholic solution of 2 per cent glacial acetic acid and 4 per cent formaldehyde at a temperature of −13°C. (kept constant with cracked ice). There it remains for from twenty to forty minutes, the time again varying with the size of the heart, or until the organ is in a firm but not frozen state. In the event that this low temperature plus acidification does not gel the compound completely, pledgets of cotton soaked in 4 per cent glacial acetic acid should be on hand to minimize leakage during the unrolling of the heart. The unrolling procedure is carried out exactly as advocated by Schlesinger.

*Roentgenography.*—Following the unrolling, the heart is x-rayed, employing the following technique: kilovolt peak, 38; milliamperes, 10; distance, 36 inches; time, 10 seconds; medium cone. An opaque marker is placed in the region of the enucleated septum, with orientating markers to designate the right and left coronary arteries. The technique is so standardized that a technician can demonstrate the wet roentgenogram approximately one to one and one-half hours after the heart has been removed.

The cannulae are then removed and the injected specimen is fixed in a 4 per cent formaldehyde solution acidified with 2 per cent glacial acetic acid. Dissection of large nonoccluded vessels at the autopsy table is not advisable because the gelling may be reversible; however, if corrosion specimens are not desired, then leakage is of no consequence and random dissection may be carried out immediately.

Corrosion specimens are adequately prepared (after fixation) by macerating the muscle tissue in concentrated hydrochloric acid (commercial) (see Fig. 7). If this is done at 56°C. in an incubator, the process may be completed in from twelve to eighteen hours. If it is desirable to clear the specimens, caution should be taken not to use rubber solvents such as xylol and benzene.

During histologic preparation, "tearing" of the section may occur when large vessels are encountered. This may be minimized by icing the block and by cutting the sections at 8 to 10 micra. Microscopic detail is well preserved.

The x-ray negatives or prints of these negatives may be incorporated into the protocol, thus providing permanent objective data for further comprehensive study.

## RESULTS

To date ten hearts have been injected with the technique described. Frozen sections cut at 12 to 16 micra have revealed consistent injection of precapillary arterioles (15 to 25 micra in luminal diameter) regardless of the time post mortem. One heart was considered inadequately injected when the cannula leading to the left coronary artery became plugged with debris from improperly cleaned tubing. Injection of the posterior leaflet of the mitral valve occurred in a heart which was

the seat of moderate aortic stenosis (Fig. 4). An instructive corrosion specimen was prepared from one injected heart (Fig. 5) with the demonstration of the circulation from the cannulated accessory right coronary ostium.

## SUMMARY

The need for an objective, rapid, and complete method of routinely studying the coronary arterial circulation post mortem is presented with suggestive lines of investigation. A technique so qualified which combines natural latex as injection compound with Schlesinger's method of unrolling the heart is described. A method of cooling is described which facilitates the setting of the injection mass. A method of preparing cannulae is also given.

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# FURTHER OBSERVATIONS ON THE TREATMENT OF THE ANGINAL SYNDROME WITH THIOURACIL

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RAAB[1] and Ben-Asher,[2] in 1945, reported on the observation, made independently, that thiouracil is effective in the treatment of the anginal syndrome. Of the ten patients with angina pectoris treated with the drug, Raab found that seven showed clinical impovement. In the eight patients that the author treated, the results obtained were excellent in two, good in five, and fair in one.

The explanation for the beneficial results obtained with thiouracil in angina pectoris is probably the same as for total thyroidectomy. Levine and Eppinger[3] believe that thyroidectomy results in an alteration in the sensitivity of the heart to adrenalin. These authors found that the rise in blood pressure and pulse rate, induced by the intramuscular injection of adrenalin, was greatly diminished when the test was performed after total thyroidectomy. They also have shown that in patients in whom adrenalin produced an attack of angina pectoris the injection did not cause an attack after the operation. They, therefore, conclude that the improvement following thyroidectomy may be brought about by the diminished sensitivity of the heart to adrenalin, as well as by the decrease in the work of the heart resulting from a fall in the basal metabolic rate. As further evidence to support this theory, Raab[4] found that thyroxin sensitizes the heart in the rat to epinephrine and that pretreatment with thiouracil reduces the sensitivity.

Shambaugh and Cutler[5] suggest that the therapeutic results of thyroidectomy in angina pectoris may be due to an interference with the thyroadrenal mechanism. Anginal pains are frequently associated with a rise in blood pressure and pulse rate caused by a sudden increase in the secretory activity of the adrenals. The beneficial results of thyroidectomy, they suggest, may be due to a diminished effectiveness of the physiologic output of adrenalin.

The advantage of reducing the function of the thyroid with a drug rather than by a radical surgical procedure is obvious. It is the purpose of this paper to present the results of treatment with thiouracil in twenty-nine additional patients with angina pectoris as well as to report on a follow-up of the patients described in the first report.[2]

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From the cardiac clinics of the Medical Center and the Greenville Hospital, Jersey City, N. J.
The thiouracil was supplied by Dr. Stanton M. Hardy of the Lederle Laboratories, Inc., Pearl River, N. Y.
Received for publication Sept. 20, 1946.
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## MATERIAL AND METHOD

Twenty-nine patients, twenty-four men and five women, with angina pectoris were studied at the cardiac clinics of the Jersey City Medical Center and the Greenville Hospital. This makes a total of thirty-seven patients thus far treated with thiouracil. The ages varied from 42 to 69 years. All had had angina pectoris for a period of time, varying from eight months to nine years. Thirteen patients had a history of an old coronary occlusion.

Each patient had a complete history, physical examination, blood count, and basal metabolism test before treatment was begun. In some patients blood cholesterol determinations were made before and during treatment. All of them were observed for one to two months before treatment. Blood counts were made once or twice weekly for the first two months and later were made at longer intervals.

The patients were divided into two groups. In one (Group A), studied in the early period of this investigation, twenty patients received an initial daily dose of 0.6 Gm. of thiouracil by mouth until clinical improvement was noted. This dose was given for two to three weeks, after which the patients were placed on a daily maintenance dose of 0.1 to 0.2 Gm. for a period varying from three to seven months. In the second group (Group B), the initial daily dose was 0.4 Gm. followed by a maintenance dose of 0.1 to 0.2 Gram.

In order to eliminate the possibility of suggestion, twelve patients received a placebo in the course of this study. This consisted of tablets which looked like thiouracil in size and shape. In eight patients the course of treatment was interrupted by the placebo for periods of two to eight weeks. Four patients received the placebo at the completion of treatment for periods of six weeks to four months.

The patients were instructed to continue their previous activities, if possible, and to report at each visit (1) the number of anginal attacks experienced, (2) the severity and duration of each attack, (3) the amount of physical activity before the attack occurred, and (4) the number of nitroglycerine tablets used since the last visit.

In order to obtain objective data, standardized exercise tolerance tests, as described by Master,[6] were performed on ten patients before treatment and at frequent intervals during the investigation. This consisted of ascending and descending a two-step staircase and noting the number of ascents necessary to induce substernal or precordial discomfort. Each test was made at least two hours after a light meal. The room temperature was kept between 72° and 76°F.

The results were classified as excellent, good, fair, and poor according to the criteria which follow. The results were regarded as *excellent* if (1) the patient did not experience any precordial distress in the course of normal activities, (2) there was an increase of 100 per cent or more in the exercise tolerance test. The results were regarded as *good* if (1) mild pain occurred infrequently, (2) there was an increase of at least 100 per cent in physical activities, (3) there was an increase of at least 50 per cent in the exercise tolerance test. The results were regarded as *fair* if (1) there was an increase of 50 per cent in the normal physical

TABLE I. RESULTS IN TWENTY PATIENTS (GROUP A) WITH ANGINA PECTORIS TREATED WITH AN INITIAL DAILY DOSE OF 0.6 GM. OF THIOURACIL

| CASE | NAME | AGE | SEX | DURATION OF ANGINA PECTORIS | DEGREE OF ANGINA PECTORIS | BLOOD PRESSURE | B. M. R. | | ONSET OF IMPROVEMENT (WK.) | DURATION OF TREATMENT | RESULTS | DURATION OF IMPROVEMENT AFTER DRUG WAS STOPPED (MO.) | REMARKS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | BEFORE THIOURACIL THERAPY | MAXIMUM CHANGE UNDER TREATMENT | | | | | |
| 1 | F. M. | 54 | F | 5 yr. | 4+ | 160/100 | +24 | −12 | 2 | 5 mo. | Good | 9 | Relapse eight mo. after drug was stopped; response to a second course of 0.4 Gm. |
| 2 | C. J. | 46 | M | 2 yr. | 2+ | 146/80 | +6 | −18 | 3 | 5 mo. | Good | 10 | Relapse under 2 mo. of placebo given at completion of treatment; response to second course of 0.4 Gm. |
| 3 | C. R. | 62 | M | 16 mo. | 4+ | 130/70 | +14 | −16 | 4 | 5 mo. | Excellent | 16 | Improvement maintained to date |
| 4 | R. D. | 52 | M | 9 mo. | 3+ | 160/110 | +12 | −8 | 3 | 5 mo. | Good | 8 | Relapse 5 mo. after drug was stopped; response to a second course of 0.4 Gm. |
| 5 | P. S. | 48 | M | 1 yr. | 4+ | 176/100 | +8 | −20 | 6 | 4 mo. | Good | 11 | Repalse under 6 wk. of placebo given at completion of treatment; response to a second course of 0.4 Gm. |
| 6 | C. S. | 46 | M | 15 mo. | 4+ | 120/70 | +4 | −16 | 4 | 5 mo. | Good | 15 | Improvement maintained to date |
| 7 | G. T. | 62 | M | 8 yr. | 4+ | 200/120 | +16 | −12 | 6 | 6 mo. | Fair | 15 | No change in status under 2 mo. of placebo given at completion of treatment |
| 8 | C. R. | 47 | M | 16 mo. | 3+ | 126/70 | −6 | −18 | 4 | 18 wk. | Good | 14 | Improvement maintained to date |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 9 | S. A. | 69 | M | 1 yr. | 3+ | 218/110 | +18 | — | — | 2 days | Poor | — | Thiouracil stopped on third day because of fever |
| 10 | H. D. | 44 | M | 6 yr. | 2+ | 120/80 | +11 | −27 | 1 | 7 mo. | Excellent | 7 | Relapse when course was interrupted by 3 wk. of placebo |
| 11 | B. P. | 43 | M | 30 mo. | 4+ | 146/80 | +10 | −15 | — | 6 mo. | Poor | — | Symptoms of myxedema; status unchanged with treatment |
| 12 | C. E. | 54 | M | 2 yr. | 3+ | 160/90 | +6 | — | — | 1 wk. | Poor | — | Died of coronary occlusion in second week of treatment |
| 13 | F. N. | 66 | F | 1 yr. | 2+ | 190/110 | −4 | −13 | 2 | 7 mo. | Good | 5 | Relapse when course was interrupted by 6 wk. of placebo |
| 14 | J. M. | 44 | M | 20 mo. | 3+ | 120/80 | +12 | −24 | 2 | 6 mo. | Excellent | 7 | Symptom free; increase in number of ascents 155% |
| 15 | F. Y. | 57 | M | 9 yr. | 4+ | 160/96 | +16 | — | — | 9 days | Poor | — | Thiouracil stopped on tenth day because of fever |
| 16 | M. C. | 48 | M | 30 mo. | 3+ | 140/80 | +8 | −20 | 3 | 13 wk. | Fair | 8 | Thiouracil stopped in fourteenth week because of neutropenia |
| 17 | F. P. | 64 | M | 2 yr. | 4+ | 230/120 | +12 | −28 | — | 6 mo. | Poor | — | Status unchanged with treatment |
| 18 | W. R. | 58 | M | 15 mo. | 4+ | 120/80 | +21 | — | — | 2 days | Poor | — | Thiouracil stopped on third day because of fever |
| 19 | S. J. | 42 | M | 4 yr. | 3+ | 140/76 | +16 | −18 | 1 | 6 mo. | Excellent | 5 | Improvement maintained to date |
| 20 | M. M. | 66 | M | 2 yr. | 2+ | 180/100 | +14 | −6 | 2 | 3 mo. | Good | 6 | Thiouracil stopped in thirteenth week of treatment because of neutropenia |

The first eight cases were described in a previous paper.

TABLE II. RESULTS IN SEVENTEEN PATIENTS (GROUP B) WITH ANGINA PECTORIS TREATED WITH AN INITIAL DAILY DOSE OF 0.4 GM. OF THIOURACIL

| CASE | NAME | AGE | SEX | DURATION OF ANGINA PECTORIS | DEGREE OF ANGINA PECTORIS | BLOOD PRESSURE | B. M. R. | | ONSET OF IMPROVEMENT (WK.) | DURATION OF TREATMENT | RESULTS | DURATION OF IMPROVEMENT AFTER DRUG WAS STOPPED (MO.) | REMARKS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | BEFORE THIOURACIL THERAPY | MAXIMUM CHANGE UNDER TREATMENT | | | | | |
| 21 | G. L. | 60 | M | 3 yr. | 2+ | 130/86 | +12 | -13 | 3 | 7 mo. | Good | 6 | Relapse when course was interrupted by 4 wk. of placebo |
| 22 | F. P. | 45 | F | 8 mo. | 2+ | 146/90 | +8 | −26 | 2 | 6 mo. | Excellent | 5 | Symptom free; increase of 118% in number of ascents |
| 23 | J. C. | 57 | M | 2 yr. | 4+ | 220/140 | −7 | — | — | 6 mo. | Poor | — | Status unchanged with treatment |
| 24 | M. L. | 50 | F | 18 mo. | 3+ | 176/100 | +14 | +2 | 6 | 5 mo. | Fair | 4 | Status unchanged under 4 mo. of placebo given at completion of treatment |
| 25 | T. P. | 61 | M | 2 yr. | 3+ | 160/110 | +39 | — | — | 6 days | Poor | — | Thiouracil stopped on seventh day because of fever |
| 26 | L. G. | 44 | M | 9 mo. | 4+ | 120/76 | −5 | −20 | 5 | 6 mo. | Good | 4 | Symptom free; increase in number of ascents only 71% |
| 27 | C. T. | 62 | M | 1 yr. | 4+ | 166/90 | +12 | −4 | — | 6 mo. | Poor | — | Status unchanged with treatment |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 28 | E. C. | 47 | M | 6 yr. | 3+ | 140/80 | +6 | −26 | 3 | 7 mo. | Excellent | 3 | Relapse when course was interrupted by 3 wk. of placebo |
| 29 | H. R. | 63 | F | 20 mo. | 2+ | 200/100 | −2 | −18 | 3 | 6 mo. | Good | 2 | Relapse when drug was interrupted by 2 wk. of placebo |
| 30 | M. R. | 59 | M | 10 mo. | 3+ | 146/90 | +8 | −20 | 6 | 6 mo. | Fair | 2 | Status unchanged when ocurse was interrupted by 2 mo. of placebo |
| 31 | J. N. | 52 | M | 4 yr. | 3+ | 150/86 | −6 | −24 | — | 6 mo. | Poor | — | Status unchanged with treatment |
| 32 | S. R. | 43 | M | 15 mo. | 4+ | 130/70 | +16 | −8 | 3 | 6 mo. | Excellent | 3 | Symptom free; exercise tolerance test increased 132% |
| 33 | H. G. | 48 | M | 1 yr. | 3+ | 186/70 | +7 | −27 | 5 | 7 mo. | Good | 2 | Relapse when course was interrupted by 4 wk. of placebo |
| 34 | L. C. | 58 | M | 18 mo. | 4+ | 216/120 | +10 | −14 | — | 6 mo. | Poor | — | Symptoms of myxedema; status unchanged with treatment |
| 35 | S. L. | 44 | F | 16 mo. | 3+ | 140/76 | −4 | −12 | 4 | 15 wk. | Fair | 3 | Thiouracil stopped in sixteenth week because of neutropenia |
| 36 | E. P. | 49 | M | 3 yr. | 3+ | 160/90 | +24 | +8 | 3 | 7 mo. | Good | 2 | Relapse when course was interrupted by 6 wk. of placebo |
| 37 | M. H. | 60 | M | 2 yr. | 4+ | 206/112 | +9 | — | — | 4 days | Poor | — | Thiouracil stopped on fifth day because of fever |

activity before the occurrence of pain, (2) there was an increase of 25 per cent in the exercise tolerance test. The results were regarded as *poor* when these criteria were not met.

## RESULTS

*Results Based on Subjective Response.*—In Table I is shown the result of treatment of twenty patients with angina pectoris with an initial daily dose of 0.6 Gm. of thiouracil. Definite clinical improvement was obtained in fourteen patients (70 per cent). In these fourteen patients, the results were excellent in four, good in eight, and fair in two. The onset of improvement occurred within one to six weeks. The average was three weeks. The average duration of treatment was 5.2 months. Improvement has been maintained for five to sixteen months after thiouracil was discontinued. Four of five patients in this group had relapses when placed on a placebo. In two the relapses occurred when the course of treatment was interrupted by a placebo, and two had relapses when placed on a placebo at the completion of treatment. In one the status remained unchanged when the placebo was administered at the end of treatment. The four who had relapses responded to a second course of 0.4 Gm. of thiouracil as an initial dose.

In one patient (Case 20) the drug was stopped in the thirteenth week and in another (Case 16) in the fourteenth week of treatment because of neutropenia.

Of the five patients in whom the results were classified as poor, the drug was discontinued in two on the third day and in one on the tenth day because they developed fever. One patient who had evidence of an old myocardial infarction died of a coronary occlusion in the second week of treatment.

Of the eight patients described in a previous report relapses occurred in two patients. In one patient (Case 1) the relapse occurred eight months after the drug was discontinued and in the second (Case 4) five months after cessation of treatment. Both responded to a second course consisting of 0.4 Gm. of thiouracil as an initial dose. The result in Case 1, previously regarded as excellent, is now regarded as good.

Table II gives the result of treatment in seventeen patients who received an initial dose of 0.4 Gm. of thiouracil. These patients were studied in the later period of this investigation. Clinical improvement was evident in eleven patients (64 per cent). Of these eleven, the results were excellent in three, good in five, and fair in three. The onset of improvement occurred within two to six weeks. The average was 3.9 weeks. The average duration of treatment was 5.9 months. In these, improvement has been maintained for two to six months after the drug was discontinued. Relapses occurred in five of seven patients who were placed on a placebo. In these five, the relapse occurred when the course of treatment was interrupted by the placebo. Of the two in whom the status remained unchanged, one received the placebo during the course of treatment and the other received it at the end of treatment. The five patients who had relapses responded to a second course of thiouracil.

In two patients in this group the drug was stopped because of a fever. In one (Case 37) the fever occurred on the fifth day, and in the second (Case 25) on the seventh day of treatment. In one patient (Case 35) thiouracil was discontinued in the sixteenth week of treatment because of the development of neutropenia.

Improvement has been maintained for from three to six months in the three patients in both groups who developed neutropenia in the fourth month of treatment. The results in both groups thus treated were excellent in seven, good in thirteen, fair in five, and poor in twelve.

*Results Obtained with the Standardized Exercise Tolerance Test.*—Table III shows the results of this test before treatment and at the time of maximum improvement with thiouracil. In three patients there was an increase of more than 100 per cent in the number of ascents, in five patients the increase was more than 50 per cent, in one patient it was more than 25 per cent, and in two patients it was less than 25 per cent. In one patient (Case 26) who was symptom free under normal activities the increase in the number of ascents was only 71 per cent.

TABLE III. RESULTS WITH STANDARDIZED EXERCISE TOLERANCE TEST

| CASE | AVERAGE NUMBER OF ASCENTS | | INCREASE (PER CENT) |
|---|---|---|---|
| | BEFORE TREATMENT | AT TIME OF MAXIMUM IMPROVEMENT | |
| 11 | 15 | 18 | 20 |
| 13 | 17 | 25 | 64 |
| 14 | 20 | 51 | 155 |
| 16 | 18 | 24 | 33 |
| 20 | 24 | 41 | 79 |
| 21 | 28 | 47 | 60 |
| 22 | 21 | 49 | 133 |
| 26 | 14 | 24 | 71 |
| 32 | 16 | 39 | 132 |
| 34 | 13 | 15 | 15 |
| 36 | 18 | 31 | 72 |

*Changes in the Basal Metabolic Rate.*—Before treatment the basal metabolic rate varied from —7 to +39 per cent. With thiouracil therapy the range was between +8 and —28 per cent.

In ten patients of Group A and in seven of Group B the basal metabolic rate was less than —15 per cent. Although there was generally a reduction in the basal metabolic rate with thiouracil treatment, the fall did not always correspond with the clinical result. In one patient (Case 17) in whom the result was classified as poor, the basal metabolic rate before treatment was +12 per cent; under thiouracil the basal metabolic rate fell to —28 per cent. In another patient (Case 32) in whom the result was classified as excellent, the basal metabolic rate before treatment was +16 per cent, and at the time of maximum improvement it was only —8 per cent.

*Changes in the Blood Cholesterol.*—Determinations of the blood cholesterol were made on ten patients. The results are shown in Table IV. Before treatment the blood cholesterol varied from 174 to 216 mg. per cent. The average was 197 mg. per cent. With thiouracil, the range was between 224 and 446 mg. per cent. The average was 278.6 mg. per cent. Here also the rise in blood cholesterol did not always correspond with the clinical result. In Case 19, in which the result was classified as excellent, there was an increase of 50 mg. per cent. In Case 34, in which the increase in blood cholesterol was equivalent to 252 mg. per cent, and in which symptoms of myxedema developed, the clinical response was poor.

TABLE IV. EFFECT OF THIOURACIL TREATMENT ON BLOOD CHOLESTEROL

| CASE | BLOOD CHOLESTEROL (MG. PER CENT) | |
|---|---|---|
| | BEFORE TREATMENT | MAXIMUM CHANGE WITH TREATMENT |
| 10 | 196 | 272 |
| 13 | 210 | 258 |
| 19 | 174 | 224 |
| 21 | 182 | 230 |
| 26 | 208 | 274 |
| 29 | 190 | 262 |
| 30 | 216 | 288 |
| 32 | 188 | 238 |
| 34 | 194 | 446 |
| 35 | 212 | 294 |

*Effect on the Electrocardiogram.*—A diminution of 2 mm. in $T_1$ was noted in five patients. In nine patients $T_1$ and $T_2$ were lowered 1 millimeter. An elevation of 2 mm. in $T_1$ and of 3 mm. in $T_4$ occurred in three patients. The typical low voltage of the QRS complexes described in myxedema was not noted.

*Effect on Weight and Blood Pressure.*—An average increase of 6 pounds in weight was noted in eighteen patients under thiouracil therapy. This increase occurred largely in the third month of treatment. No appreciable effect on the blood pressure was noted.

*Reaction to Thiouracil.*—Toxic effects were noted in eight patients treated with thiouracil. Of these, five patients developed fever. In Group A, two patients had a fever on the third day and one patient on the tenth day of treatment. In Group B, one patient had fever on the fifth day and another on the seventh day of treatment. The temperature became normal when the drug was discontinued. Neutropenia was noted in three patients. In Group A, one patient developed neutropenia in the thirteenth week and another in the fourteenth week of thiouracil therapy. One patient in Group B developed neutropenia in the sixteenth week of treatment. The white count returned to normal spontaneously when the drug was stopped.

## COMMENT

These studies which have extended over a period of thirty-two months confirm the observation that thiouracil is effective in the treatment of the anginal syndrome. The fact that relapses occurred in nine of the twelve patients placed on a placebo, as well as the results obtained from the standardized exercise tolerance test, eliminate the possibility of suggestion as a factor in the therapeutic response.

The danger of toxic reactions is, however, a definite drawback in the use of the drug in angina pectoris, as it is in hyperthyroidism. In this series, fever and neutropenia were the only ill effects noted. Agranulocytosis, a more serious reaction reported in the literature, was not encountered. Although encouraging results have recently been obtained in treating this reaction with penicillin,[7-9] all patients receiving thiouracil should be carefully observed, particularly with reference to the blood.

One must also consider the ill effects of hypercholesterolemia on the coronary arteries resulting from the thiouracil therapy. Further studies are necessary to determine the role of cholesterol in the pathogenesis of artereosclerosis.

## SUMMARY AND CONCLUSIONS

1. Thiouracil was found to be beneficial in twenty-five of thirty-seven patients (67 per cent) with the anginal syndrome.

2. Definite improvement was obtained in fourteen of twenty patients (70 per cent) receiving an initial daily dose of 0.6 Gm. of thiouracil. The onset of improvement began, on the average, after three weeks of treatment.

3. Eleven of seventeen patients (64 per cent) improved with an initial daily dose of 0.4 Gm. of thiouracil. The onset of improvement averaged 3.9 weeks.

4. Five patients developed fever in the first ten days of treatment.

5. Three patients developed neutropenia in the fourth month of treatment.

6. Thiouracil is an effective drug in the treatment of angina pectoris. The smaller dose (0.4 Gm.) is almost as effective as the larger dose (0.6 Gm.). Toxic reactions may occur with both.

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# RAYNAUD'S DISEASE IN MEN

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THE vasospastic disorders are a group of peripheral vascular disturbances in which the arterial circulation is impaired, either intermittently and spasmodically or more or less continuously, as a result of tonic contractions of blood vessels. They are differentiated from the obliterative arterial diseases by the general absence of pathologic changes in the walls of the arteries, leading to narrowing or occlusion of the lumen, except in those instances in which the process is long continued or very severe.

Of the group of vasospastic conditions, the clinical entity which is best known was first described by Raynaud[1a] in 1862 and has since been designated by his name. In the interval a great number of reports have appeared in the literature indicating a wide divergence of opinion as to what criteria are necessary for the diagnosis of Raynaud's disease. Some workers have grouped together loosely a variety of circulatory disorders in which there is present as a common feature an abnormal responsiveness to cold. Others have attempted to limit the term Raynaud's disease rigidly to a progressive disorder without preceding local injury or disease which possesses the following characteristics: it occurs primarily in women, with onset in the second or third decade, and is typified by intermittent episodes of symmetrical blanching or cyanosis of the fingers and toes, and occasionally of the tips of the nose and ears, as a result of exposure to cold or emotional excitation. A popular concept has arisen that a triphasic color reaction is an essential component of Raynaud's disease; namely, blanching, followed by cyanosis, and then rubor as the attack passes away. Beginning with Raynaud[1] himself, however, numerous students[2-5] of this malady have recognized that the initial color change may be either pallor or cyanosis.

Since a typical color response to cold or emotion may also occur as part of the clinical picture of a variety of conditions, it has been suggested that all patients showing this type of response as a secondary manifestation should be classified under Raynaud's syndrome or phenomenon. The term Raynaud's disease should then be reserved for those cases in which no etiology can be dis-

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covered and which have showed intermittent episodes of digital syncope or cyanosis for a relatively long period of time (at least two years) without the appearance of any signs of occlusive arterial disease.[6]

The present report deals with an analysis of fifty cases of Raynaud's disease in men, as studied in a Center set up by the Army for the care of patients with vascular disorders. For the most part, the clinical stories of the individuals in the group conform to the rigid criteria previously enumerated, except that in approximately one-half of the patients the condition had existed for less than two years at the time of their hospitalization. Not included in the series are all instances of Raynaud's syndrome observed in men in whom frostbite, local trauma, or the use of vibrating tools appeared to be the causative factor; these cases were otherwise identical in symptomatology and physical findings. Those patients who demonstrated typical manifestations but in whom there was the slightest suspicion that organic vascular disease was the basis for these responses were likewise omitted from the group.

Since most observers have reported that primary Raynaud's disease occurs almost exclusively in women, a general feeling has arisen that the disorder is extremely rare in men and that such a diagnosis is very likely to be in error. The purpose of this study, therefore, is to emphasize the recent observation of Hines and Christensen,[7] that typical Raynaud's disease does exist in men as well as in women and, in addition, to point out that the types of cases observed under the stress and strain of Army life are no different from those seen in civil life.

## CLINICAL RESULTS

In every patient in the series, either the color change had been noted by the attending medical officer during the present hospitalization or in previous medical installations, or the occurrence of this phenomenon was so regular and so clear cut that its existence could be established through interrogation. Four of the group were Negroes; the remaining forty-six patients were white. The age of the patients ranged from 21 to 51 years, the average age being 29.5 years. In twenty the disorder was of one year's duration or less, in six it had been present from one and one-half to two years, and in the remaining twenty-four it had existed for from two to thirteen years. In the great majority of patients the first attack occurred during cold weather; in a few it appeared in cool weather. Many of the patients were either civilians at the time or were in the Army but were still in the United States. In only one patient did the symptoms first arise either immediately before or during conditions of combat. The critical temperature subsequently necessary to initiate an attack varied widely, some patients undergoing blanching in slightly cool weather, others only during severe cold. Immersion of limbs in cold water or even ice water was much less effective in eliciting the response than was exposure of the body to a low environmental temperature. In fourteen patients some neuropsychiatric background or emotional instability was found, but in only one of these were the attacks of digital pallor brought on

by emotion. Of the remaining thirty-six patients, in whom no psychiatric stigmas were observed, this stimulus was effective, nevertheless, in producing the typical color changes in four.

Twenty-five of the fifty patients studied showed all the features which have been considered classical. On exposure to cold, the involved digits would turn dead white and the patient would have a feeling of intense coldness, numbness, and stiffness. Generally a clear-cut line of demarcation was present between the portion of the digit showing the pallor and that manifesting a normal color of the skin. On exposure to a warm environment, the digits would become cyanotic after a varying interval, rubor would follow, and then the normal color would return. In the later stage of the attack most of the patients would complain of tingling, throbbing, burning, or other paresthesias.

In the remaining twenty-five patients in this group the triphasic color reaction was not present. In nine cyanosis alone followed the blanching, with a subsequent return to normal color, ten showed rubor immediately after the pallor but with no intervening noticeable cyanosis, four demonstrated the blanching alone, followed directly by return of normal color, one demonstrated cyanosis and then restitution of normal color, and one demonstrated cyanosis followed by rubor without pallor. In all instances, however, the initial response was either pallor or cyanosis, pallor being much more frequent.

Syncope involved varying segments and numbers of digits. In some patients only the tips of the fingers or toes were affected; in others the change occurred either in the distal phalanx, the distal two phalanges, or in the entire digit. All four extremities were involved in five patients, both hands and one foot in two, both hands in thirty-five, one hand in five, one hand and both feet in one, the two feet in one, and one foot in one patient.

Asymmetrical distribution of the color changes in the two limbs was noted in twelve patients. Of this number, six exhibited pallor in one or several digits of a single extremity only, while in six there was asymmetry of involvement of the two paired limbs. In the remaining thirty-eight patients symmetrical changes were noted. In three of these, all ten digits of the hands and feet were involved; in four, all fingers of the two hands; in fourteen, the second, third, fourth, and fifth fingers of the two hands; and in one, all ten toes. It must be pointed out that in a number of the patients demonstrating symmetrical involvement, the history revealed that first one or two digits in a single extremity showed the change and that subsequently there was a progressive spread to other portions of the hand or foot and eventually to the contralateral limb.

The presence of symptoms was not always coincident with the actual occurrence of blanching. In fact, a number of patients had experienced numbness, coldness, stiffness, and paresthesias in the involved limbs years before the onset of the episodes of color changes. In some, although the symptoms were generally worse on the side exhibiting the attacks of pallor or cyanosis, exposure to cold frequently elicited similar complaints in the contralateral limb, in which color changes did not occur.

In the interval between attacks many of the patients were asymptomatic and maintained a normal circulation. However, about one-half of them dem-

onstrated some evidence of excessive sympathetic activity. This manifested itself as either cool, moist, and slightly cyanotic hands or feet or only coolness and excessive sweating. In some instances, moderate hyperhidrosis was noted without any alteration in cutaneous temperature or skin color.

Trophic changes occurred in eight patients. Generally they were slight and consisted only of some distortion of the nails or minimal thickening of the skin. However, in some the skin covering the finger tips seemed actually to be separated from the deeper tissues, and pressure applied to it would produce a temporary dimpling (Fig. 1). One patient demonstrated bilateral gangrene of the finger tips of a limited extent (Fig. 2,*A*). It is of interest that in two patients trophic changes occurred very early in the disease. One of these deserves further men-

Fig. 1.—Fairly recent case of Raynaud's disease, showing dimpling of skin of tip of thumb after application of pressure. Phenomenon is due to loss of subcutaneous tissue.

tion. This individual was a 21-year-old man without previous vascular manifestations who had developed sensitivity to cold only three weeks before admission. While exposing his hands to a low external environment, he observed the right second, fourth, and fifth fingers to become very cyanotic, intensely cold, and uncomfortable. When he returned indoors the hand became warm and some time later the cyanosis and discomfort disappeared. Thereafter coldness, blueness, and some numbness of the fingers of both hands occurred on exposure to cold, with discomfort limited to the right hand. When examined upon admission, the hands were found to be cool and moist and the finger tips, with the exception of the thumbs, already showed thickening of the skin and striking loss of subcutaneous pulp, so that the skin dimpled upon pressure. This change was more obvious in the right index finger, which was the digit most sensitive to cold. Exposure of the hands to a low environmental temperature brought about intense cyanosis of the fingers.

Examination of the peripheral circulation in a warm environment consistently revealed no abnormalities in any of the patients in the group. All the pulses were readily palpable in the extremities, except for the occasional absence of the

dorsalis pedis pulse on one or both sides. No signs of arteriosclerosis were noted. Similarly, the various simple procedures for the determination of the state of the circulation, such as the plantar pallor test, the venous filling time, oscillometry, and the production of local vasodilatation through body heating or paravertebral sympathetic block with procaine, all indicated that no organic vascular disease existed.

*A.*

**Fig. 2.—*A*. Case of long-standing Raynaud's disease showing bilateral superficial gangrene of finger tips.**

*B.*

***B*. Complete healing of ulcerative areas shortly after bilateral dorsal sympathectomy.**

## TREATMENT

The majority of the patients in this series were not treated actively but were advised to stop smoking, to attempt to control their emotions if these played a role in precipitating the color changes, to live in a warm environment if possible, to try to avoid exposure to cold, and to dress warmly if this were not feasible. Sympathetic ganglionectomy was resorted to if the number and severity of the attacks were distressing or incapacitating or if nutritional disturbances existed. The operation was performed upon seven patients, fourteen extremities being sympathectomized. All four limbs were denervated in one patient; both upper limbs were denervated in three; both upper limbs and one lower limb in one; and one upper limb was denervated in two patients. In all patients except possibly one the immediate therapeutic effects were excellent. In the exception, all four extremities were sympathectomized in four stages. Although at each operation the patient felt sufficiently relieved to desire to have the next, at the completion of the procedure he was in doubt as to the total benefit. He no longer had any attacks of digital syncope and demonstrated a relatively stable circulation in his extremities, but he stated that he had some tingling in cold weather and annoying, and at times incapacitating, hyperhidrosis of the trunk in warm weather. The remaining patients upon whom this therapeutic procedure was done subsequently developed warm, dry, well-colored extremities, which tended to cool slowly upon exposure to cold. For the most part, attacks of syncope were absent. Those patients with loss of pulp in the tips of the fingers had a striking restoration to normal following operation. The patient with gangrene of several fingers showed prompt healing of the lesions (Fig. 2,*B*).

## DISCUSSION

It has been the general impression that transient episodes of color changes in the digits in the male are usually secondary manifestations of occlusive arterial disease. This opinion, however, is not supported by the observations in the present series or in one previously reported.[7] In no instance was there any indication that obliterative arterial disease existed or that it might subsequently appear. Such results would therefore be in accord with the view that in the differential diagnosis of peripheral vascular disorders in men manifesting color changes, the possibility of Raynaud's disease should not be disregarded.

The question whether the stress and strain of Army life may have contributed to the precipitation of this disorder in our group of patients cannot be fully answered by an analysis of the data, although it appears unlikely that this factor played an important role. In a considerable number of individuals the attacks began in civil life, and in only one instance did they arise under conditions of combat or just prior to such activity. Emotional stress and excitement initiated the color changes in only five patients, or 10 per cent, of the series, while emotional instability or other neuropsychiatric disorders were found in 28 per cent. These figures are not dissimilar to those of Hines and Christensen,[7] who reported that in only nine of their 100 male civilian patients did an attack result from emotional excitation, although functional or neurotic disorders were present in twenty-nine.

Nevertheless, one cannot rule out the hypothesis that military life may have been a factor in some patients in aggravating the condition or in bringing into activity a latent disturbance, since these soldiers were exposed to cold weather to a greater extent than they might otherwise have been.

One of the criteria generally accepted as necessary in order to make a diagnosis of Raynaud's disease is the bilateral and symmetrical involvement of the extremities. In a significant number of our patients, however, there was unilaterality of involvement either in the upper or in the lower extremities. It is possible that the earlier the condition is seen, the more frequently will the attacks be noted in one limb alone.

In one-half of the patients in this series a classical triphasic color reaction was not noted, although in other respects these cases were typical examples of Raynaud's disease. Such an observation supports the concept already mentioned that in the presence of transient attacks of either digital syncope or cyanosis, brought on by exposure to cold or emotion, the possibility of a diagnosis of Raynaud's disease should be entertained, provided no etiology can be established and signs of obliterative vascular disease are absent. Furthermore, it does not appear necessary in Raynaud's disease for either the cyanosis or the pallor to be replaced by rubor as a preliminary step to the return of normal color.

With regard to the treatment of Raynaud's disease, it can be stated that the present series confirms what is generally known; namely, that if the difficulty is severe or is progressive in character, if nutritional disturbances exist, or if the process cannot be controlled by proper climate, sympathectomy offers the best means of therapy. The early results are generally excellent. However, nothing can be deduced from this study as to the duration of the good therapeutic effect. If the severity of symptoms does not make it imperative, sympathectomy of all four extremities is to be avoided, because of the discomfort which may result from the extreme hyperhidrosis of the trunk in warm weather.

## SUMMARY AND CONCLUSIONS

The present study is based upon an analysis of fifty cases of Raynaud's disease in men. In only one-half of the patients was the typical triphasic color change of pallor, cyanosis, and rubor observed. In the remaining one-half, one or even two of these responses were absent, although in each instance the initial alteration was either digital pallor or cyanosis.

Nutritional disturbances, consisting of alterations in the nails, thickening of the skin, loss of subcutaneous tissue, and ulceration and gangrene, were present in 16 per cent of the cases.

In none of the patients were signs of organic vascular disease noted.

On the basis of the available data, the conclusion is reached that the possibility of a diagnosis of Raynaud's disease should be entertained as readily in the case of men showing characteristic color changes in the digits as in women, provided no signs of arterial obliterative disease are noted.

It is not necessary for symmetry of involvement or for a triphasic color change to be present in order to make the diagnosis.

Emotion evidently plays a much less important role in eliciting the episode of color change in men than it does in women. Furthermore, the stress and strain of Army life are apparently not potent factors in the production of the disease.

With regard to therapy, sympathetic ganglionectomy is of definite value in the treatment of nutritional disturbances and in the presence of severe and incapacitating attacks, or if steady progression of the malady is noted. Under other circumstances a trial of conservative treatment is indicated.

The authors wish to express their appreciation to Captain Herbert H. Lampert and to Major Robert H. Smith for their assistance in the collection and analysis of some of the data.

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# TRAUMATIC RUPTURE OF THE AORTA

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TRAUMATIC rupture of the aorta caused by blunt force injuries is considered to be a rare occurrence. In 1919 Jaffé and Sternberg[1] reported ten examples of this lesion, five of which occurred in flying accidents. The occurrence of such ruptures is mentioned briefly in the textbooks of legal medicine.[2-4] Single cases have been reported occasionally.[5-17] Recently, McDonald and Campbell[18] again drew attention to this rare injury when they described two cases of traumatic rupture of the normal aorta in young adults.

The reason that traumatic rupture of the aorta is not better known lies in the fact that the lesion is discovered only at necropsy. The rapid death, the state of coma and shock in which the injured person remains until death, and the concomitant severe injuries of different parts of the body, which are present in all cases, make a diagnosis during life very difficult.

Traumatic rupture of the aorta is, as a matter of fact, not as infrequent as is generally believed. From approximately 7,000 autopsies performed during the six years from 1936 to 1942 at the Chief Medical Examiner's Office of New York City in the borough of Manhattan, seventy-two cases of traumatic aortic rupture were collected. The findings in these seventy-two cases will be presented and compared with the findings in twenty-four cases of spontaneous rupture of the aorta (dissecting aneurysm) which were collected from the same source.

## TRAUMATIC RUPTURE OF THE AORTA

*Age and Sex.*—Of the seventy-two cases of traumatic aortic rupture, fifty-seven occurred in men and fifteen in women. The age distribution had a wide range. The seventy-two cases included two children under 10 years of age, two adolescents under 20 years, eight adults between 20 and 30 years, eight between 30 and 40 years, twenty-two between 40 and 50 years, eleven between 50 and 60 years, ten between 60 and 70 years, seven between 70 and 80 years, and two over 80 years of age.

Forty-two of the series were less than 50 years of age and except for the results of trauma, showed no visible gross pathologic changes in the aorta. In the thirty subjects over 50 years of age, sclerotic changes of the aorta of varying degree were present.

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Received for publication May 7, 1946.

*Cause of the Injury.*—The manner in which the accidents occurred differed greatly. In fifty-one of the seventy-two cases the injury was the result of an automobile accident. More pedestrians were victims of this injury than drivers or passengers of cars. In ten of this series rupture of the aorta occurred after a fall or jump from a considerable height. Two men were run over by subway trains. Two were killed in elevator accidents when the cars fell suddenly to the ground. In three instances the thorax was crushed by a direct blunt force (crate or stone). One man died from a rupture of the abdominal aorta after he had been kicked in the abdomen. In three instances the circumstances under which the rupture occurred could not be ascertained; the bodies were found floating in water.

*Site and Direction of the Rupture.*—In sixty-one of the subjects, the aorta had ruptured in only one site (Group 1) and in eleven instances the vessel was torn in two or more sites (Group 2). In fourteen cases (eight of Group 1, six of Group 2) the rupture was situated in the ascending aorta above the aortic cusps in the area where spontaneous rupture of the aorta usually occurs. The most frequent site of traumatic rupture was at the isthmus of the aorta below the origin of the left subclavian artery at the insertion of Botalli's ligament. In forty of the cases (thirty-eight of Group 1, two of Group 2) the tear was found in this area. In fifteen cases (twelve of Group 1, three of Group 2) the descending thoracic aorta was torn between the isthmus and the diaphragmatic opening. In three cases the site of the rupture was in the abdominal aorta. The site of the second and third tear in eleven cases of Group 2 varied considerably.

In almost all instances the rupture occurred in a transverse direction through the wall of the vessel. Only a few T-shaped or longitudinal tears were encountered. In sixty-four subjects the rupture was complete and perforated all layers of the wall, including the adventitia. In eight instances the rupture was incomplete; the adventitia was still preserved and was dissected from the media by the hemorrhage resulting from the rupture.

*Concomitant Injuries.*—In all seventy-two victims of traumatic rupture of the aorta there were other injuries of the body. Fractures of the sternum alone were found in two patients, fractures of thoracic vertebrae in four, fractures of the ribs of one or both sides in twenty-six, fractures of ribs and sternum in eleven, fractures of ribs and vertebrae in nineteen, and fractures of ribs, sternum, and vertebrae in six patients. Only four patients had no fractures of the thoracic bones.

In addition to fractures of thoracic bones, fractures of the skull, the pelvis and the extremities were found frequently. The rupture of the thoracic aorta was associated in all instances with more or less extensive lacerations of internal organs including the heart, pericardium, lungs, liver, spleen, kidneys, mesentery, and bladder.

*Cause of Death and Time of Survival.*—A slight but nonfatal hemorrhage into the pericardial sac was observed in those patients in whom the rupture was just above the aortic cusps. Hemopericardium with real cardiac tamponade, a fre-

quent finding in fatal spontaneous rupture of the aorta, was observed in only one instance of traumatic rupture. Apparently a cardiac tamponade did not occur more frequently in the victims of traumatic rupture because of concomitant lacerations of heart and pericardial sac through which the blood escaped into the chest cavities or because of a rapid developing internal hemorrhage from a second tear in the aorta or from lacerations of other large blood vessels or organs (spleen, liver).

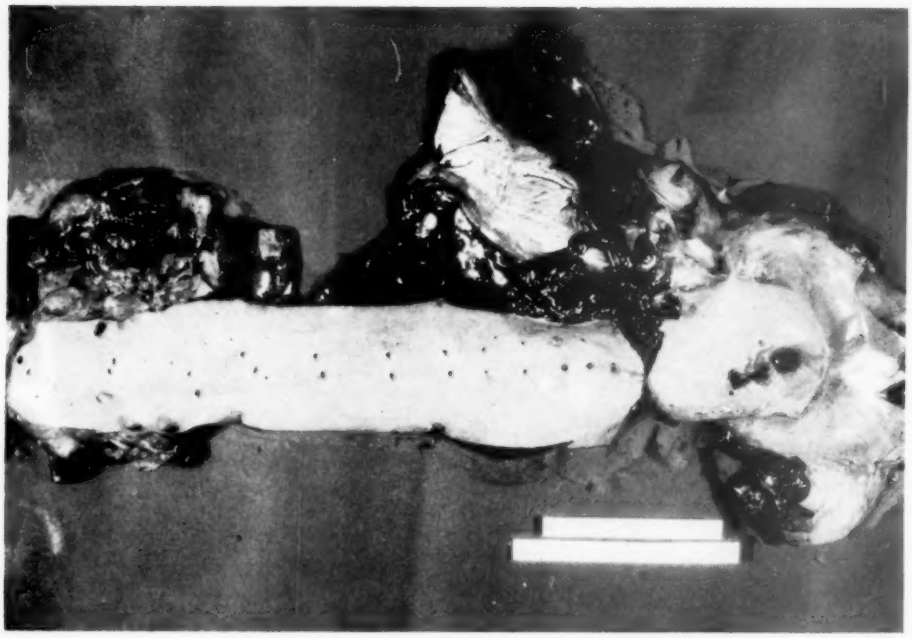

Fig. 1.—Traumatic rupture of the aorta at the isthmus in a Negro woman who was hit by an automobile and survived seven hours. (Courtesy Milton Helpern, M.D., New York, N. Y.)

The cause of death in most subjects was severe hemorrhage. In some instances the hemorrhage was the result of the aortic rupture alone; in other instances the aortic hemorrhage was associated with hemorrhages resulting from injury to other parts of the body including the heart, other blood vessels, lungs, spleen, liver, kidneys, and mesentery. In many instances fractures of the skull and (or) bones of the thorax, pelvis, and extremities were contributory factors. A ruptured thoracic aorta frequently led to a hemorrhage into the mediastinal tissue and (or) the left or both chest cavities. Hemorrhage into the retroperitoneal tissue or the abdominal cavity followed rupture of the abdominal aorta.

In fifty-nine patients death followed the injury within one hour. In all of these instances the rupture was complete and extended through all layers of the wall. Six patients lived from one to three hours, three lived from five to seven hours, and four lived from twelve to eighteen hours after the accident. In eight instances in which the victims lived for at least three hours after the injury, the rupture was incomplete in that the adventitia was intact (Fig. 1).

In contrast with the infrequent studies[1-18,34] of traumatic rupture of the aorta, spontaneous rupture, particularly in its relationship to idiopathic cystic necrosis of the media, has received wide attention.[19-33] In the autopsy material which was the source of the seventy-two cases of traumatic aortic rupture, twenty-four examples of spontaneous aortic rupture were also found. In none of the twenty-four patients was there any evidence of external trauma. Spontaneous rupture of the aorta is not the subject of this paper; however, some of the important findings in the twenty-four patients who were found to have died of this lesion will be presented so that these findings can be compared with the findings in the seventy-two patients who died of traumatic rupture of the aorta.

Eighteen of the twenty-four patients were men and six were women. The age at which death occurred ranged from 17 to 63 years. One instance of spontaneous aortic rupture occurred in a 17-year-old boy and was associated with coarctation of the aorta and a bicuspid aortic valve.[31] A bicuspid aortic valve was found in two other cases of spontaneous rupture. Eight patients who developed spontaneous rupture were in the age group between 30 and 40 years, six between 40 and 50 years, and eight between 50 and 60 years, and in one case the lesion developed in a patient who was 63 years of age.

In twenty-two instances the rupture was situated in the ascending aorta, a short distance above the aortic cusps, in one instance at the origin of the innominate artery, and in one instance at the origin of the left carotid artery. The direction of the tear was horizontal in twenty patients, L shaped in two patients, and vertical in two patients. In two patients a second tear which formed a reopening of the dissecting aneurysm into the aorta was located in the arch of the aorta.

The cause of death in all twenty-four subjects was hemopericardium which resulted from the rupture of the dissecting aneurysm into the pericardial sac. In fourteen instances death was sudden. In eight instances the victims of this lesion were found dead. As far as could be learned, they had all been in good health before death; it can be assumed, therefore, that in these eight patients death had been rapid. In two patients the time of survival was known, one man died three hours and another died twenty-two hours after the onset of symptoms.

## DISCUSSION

Necropsy studies show that the findings in the two forms of aortic rupture differ considerably. Some of these differences will be discussed.

In all of the twenty-four examples of spontaneous rupture the tear started within the media. The dissecting aneurysm which resulted ruptured into the pericardium and produced a fatal tamponade of the heart (Figs. 2 and 3).

In the seventy-two cases of traumatic rupture it was difficult to determine in which layer of the wall the rupture began, since in most instances the tear was complete and involved all layers of the wall. In a few patients who survived the accident from three to eight hours the adventitia was intact though dissected from the media by the hemorrhage which resulted from the tear. True dis-

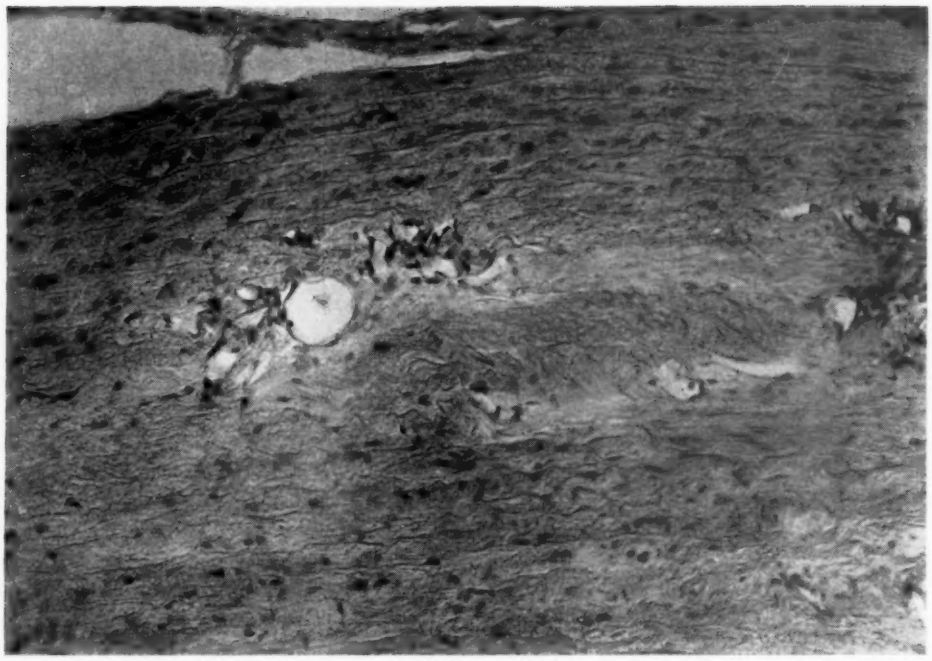

Fig. 2.—Spontaneous aortic rupture in a 50-year-old woman who was found dead. Medionecrosis cystica with mucoid degeneration. Hematoxylin and eosin stain; × 223.

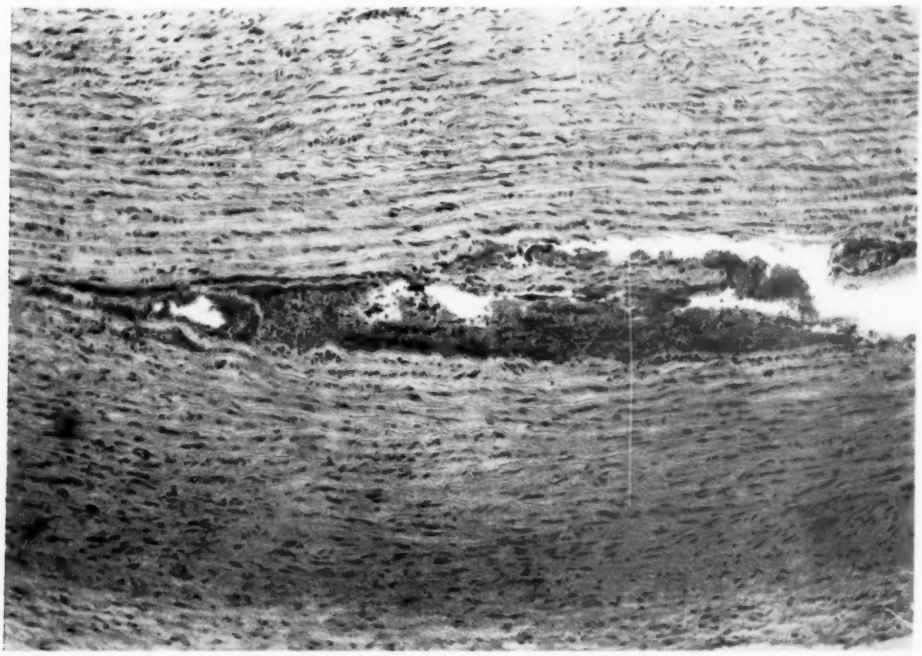

Fig. 3.—Spontaneous aortic rupture in a 50-year-old man who was found dead. Tear within the media with hemorrhage and cellular reaction. Hematoxylin and eosin stain; × 110.

section within the media (as seen in spontaneous rupture) was not found in this series of patients; apparently it is rare in traumatic rupture. It seems probable that in a number of instances of traumatic rupture the tear begins in the intima. This is suggested by the fact that in several cases superficial intimal tears were present in some areas in addition to complete tears of the whole wall. In all but two of the patients with spontaneous rupture the site of rupture was a short distance above the aortic valves. The site of traumatic rupture was not nearly so consistent: the tear occurred in various portions of the aorta but most often at the isthmus.

It is generally assumed that one factor, medial cystic necrosis, mainly determines the site of spontaneous rupture. On the other hand, many factors determine the location of aortic rupture due to trauma. A possible reason why the majority of traumatic ruptures develop at the isthmus of the aorta is the fact that the aorta is narrowed and relatively fixed at this site by the attachment of Botalli's ligament. This might render this portion of the vessel more subject to overextension or twisting or sudden increase of intra-arterial pressure. In all but four patients fractured vertebrae and (or) ribs and sternum were present. In many instances the aortic rupture was the result of laceration by sharp bone fragments. In four patients no fractured thoracic bones were present. Lacerations by sharp fragments of bones obviously did not determine the site of the rupture in all instances. Overextension or twisting of the vessel are among other possible factors. In the three patients in whom the site of rupture was in the abdominal aorta the rupture appeared to have been caused by the effect of the blunt force compressing the aorta against the vertebral column. This opinion is particularly supported by the fact that no fractures were present in one case. The same mechanism may explain the occurrence of some traumatic ruptures of the thoracic aorta. Sudden increase in intra-arterial pressure, causing a bursting rupture from within, appeared to play an important role in producing rupture of the aorta. This is the most likely explanation of the rupture in the three young patients (with elastic thoraces) in whom there were no nearby bone fractures and little evidence of external injury.

Although arteriosclerosis of the aorta was present in the older victims of traumatic rupture, the wide age distribution of the series as a whole suggests that this was not important in determining the development or the site of the aortic rupture. In three of the victims with spontaneous rupture a congenital defect was present and conceivably may have played a role in the development of the lesion. No congenital defects were present in any of the victims with traumatic rupture.

The immediate cause of death in all patients with spontaneous rupture of the aorta was a rupture of the resulting dissecting aneurysm into the pericardium and fatal cardiac tamponade. Although one patient in the series of traumatic aortic ruptures developed this lesion, the remainder of the patients died of internal hemorrhage into the chest or abdominal cavity or into retroperitoneal or mediastinal tissues.

In both forms of aortic rupture more men than women were victims of the accident. The medicolegal source of the material may have determined this fact.

The source of the material may also be responsible for the fact that healed spontaneous rupture, reports of which are not infrequent,[6,23,31,33] was not found more often in this series of patients.

## SUMMARY

Seventy-two cases of traumatic rupture of the aorta and twenty-four cases of spontaneous rupture have been reviewed and compared. The main differences regarding occurrence, origin, and pathologic picture of both lesions have been discussed.

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# Clinical Reports

## ANEURYSMAL DILATATION OF THE AORTA ASSOCIATED WITH CYSTIC MEDIAL NECROSIS

### Case Report

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SINCE Erdheim's[1,2] description of a new pathologic entity, idiopathic cystic medial necrosis of the aorta, most of the articles published on this subject have dealt with its relation to dissecting aortic aneurysms. A detailed review of this aspect of the disease may be found in the excellent articles of Sailer,[3] Rottino,[4] and Moritz.[5]

Similar pathologic lesions have been found only rarely in unruptured aortas. Rottino[6] reported seven such cases in a routine study of 210 specimens. Moritz[5] found defects of the tunica media in six of a total of seventy aortas that he studied. In these cases, as in those where dissecting aneurysms were present, the lesions were most numerous in the ascending aorta and the first part of the aortic arch. They were often, but not always, found in elderly patients with a history of antecedent hypertension.

In addition to these reports a small number of cases have been described in which cystic medial necrosis was found to be the only pathologic change in the walls of large aneurysms of the ascending aorta. The majority of these cases had associated aortic regurgitation that was clinically demonstrable. The incompetency of the aortic valve was due to the dilatation of the aortic valve ring and not to lesions of the valve cusps.

The case reported by Rottino[7] was that of a 70-year-old woman. This patient did not have aortic regurgitation. The aneurysm was 12.5 cm. in circumference and involved most of the ascending aorta. The aortic arch and aortic valve ring were involved to a much less degree. The intima was wrinkled and appeared grossly to resemble syphilitic aortitis. There was, however, no evidence of syphilitic changes when microscopic examination was made. Instead, the typical cystic areas and elastic tissue and muscle disruption of medial necrosis were found.

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Received for publication April 4, 1946.

Baer and co-workers[8] described two patients with arachnodactyly, both of whom died from cardiac decompensation due to aortic regurgitation secondary to large saccular aneurysms of the ascending aorta. One patient who died at the age of 14 years also had an associated patent foramen ovale and had been observed from birth. Cardiac murmurs had always been present. The other patient died at the age of 26 years. In neither case had the dilatation of the aorta been evident on roentgenologic examination. The circumferences of the aneurysms were 14 cm. and 19 cm., respectively. Pathologically the only lesions found to explain the presence of the aneurysms were those of cystic medial necrosis. It was the opinion of Baer and associates that this might more likely represent a congenital defect of the media rather than a degenerative process.

Another case in which arachnodactyly was present was reported by Etter and Glover.[9] Unfortunately no microscopic studies were reported so that one cannot be certain that cystic medial necrosis was present. However, the association of arachnodactyly with dilatation of the aorta, aortic regurgitation, and death, finally, due to the rupture of a dissecting aneurysm suggests that the case may belong in this group. The patient was 21 years of age at the time of death. The aortic regurgitation could have been due either to dilatation of the asecnding aorta, as in the other cases described, or to the presence of a chronic dissecting aneurysm, as in the patients described by Gouley and Anderson.[10]

Our patient failed to show arachnodactyly but the clinical and pathologic findings were strikingly similar to those described by Baer and collaborators.[8]

## CASE REPORT

E. Z., a 29-year-old white man, who worked as an attendant in a service station, entered the Los Angeles County General Hospital on July 18, 1945. The chief complaints were shortness of breath for four weeks and swelling of the legs for two weeks. He stated that he first learned that he had heart disease in 1942, when he was rejected by the Army for that reason. Since that time he had noticed palpitation of the heart and attacks of dyspnea that occurred about once a month. These were not accompanied by edema or fever and were not incapacitating. During the four weeks before admission he had experienced severe weakness and dyspnea on exertion which had forced him to cease working. Gradually the dyspnea increased until it was present at rest; for the last two weeks he had noticed edema of the feet and legs which slowly extended to the thighs and scrotum. He had a cough which had been productive of small amounts of blood-tinged sputum. He consulted his family doctor who advised admission to the hospital. He stated that he had had asthma most of his life. The attacks had been more severe and frequent since the age of 13 years and seemed to be precipitated by exposure to dust and grain. There was no history of familial disease except that his brother also had asthma. His mother had died during the influenza epidemic of 1918. The patient denied any history of rheumatic fever, rheumatic symptoms, syphilis, or antisyphilitic therapy. His only previous illnesses were rubeola as a child and pneumonia in 1937. He had had a tonsillectomy at the age of 10 years. He considered that he had had a healthy childhood and had always been able to exercise as long and as hard as other children of his age.

Examination revealed a fairly well-developed and well-nourished young man who was orthopneic and dyspneic. The vital signs were pulse, 120; temperature, 98.6; respirations, 24 per minute; and blood pressure, 115/50 in the right arm. The eyes showed slight but definite arcus senilis bilaterally. The fundi were normal. There were numerous expiratory asthmatic wheezes throughout both lung fields and inspiratory subcrepitant râles and rhonchi at both lung bases. The heart was markedly enlarged. The point of maximum impulse was visible and palpable in

the sixth intercostal space at the anterior axillary line. There was a palpable systolic thrill over the sternum. The rhythm was that of sinus tachycardia. The first sound was reduplicated over the whole precordium. At times a gallop rhythm was heard. There was a short rough systolic murmur at the aortic area with a loud blowing diastolic murmur that radiated down the left sternal border. There was a loud rough systolic murmur at the apex. The pulse was of the water-hammer type and Duroziez's murmur was prominent over the peripheral vessels. The brachial arteries were easily compressible. The liver edge was palpable 10 cm. below the right costal margin. The abdomen was slightly distended and signs of free peritoneal fluid were present. No other abdominal organs or masses were palpable. Scrotal edema and pitting edema of the feet, legs, and thighs were present. The reflexes were physiologic.

Hemoglobin was 14.0 Gm. per 100 c.c.; erythrocytes, 4,300,000 per cubic millimeter; and leucocytes, 8,550 per cubic millimeter. The differential count was normal. Sedimentation rate (Wintrobe) was 1 mm. per hour. Examination of the urine was normal. Blood chemistry was as follows: nonprotein nitrogen, 40 mg. per 100 c.c.; blood chlorides (as NaCl), 480 mg. per 100 c.c.; albumin: globulin ratio, 4.7/2.2 Gm. per 100 cubic centimeters. Blood Kolmer and Kahn reactions were negative. Blood culture showed no growth. An electrocardiogram is shown in Fig. 1.

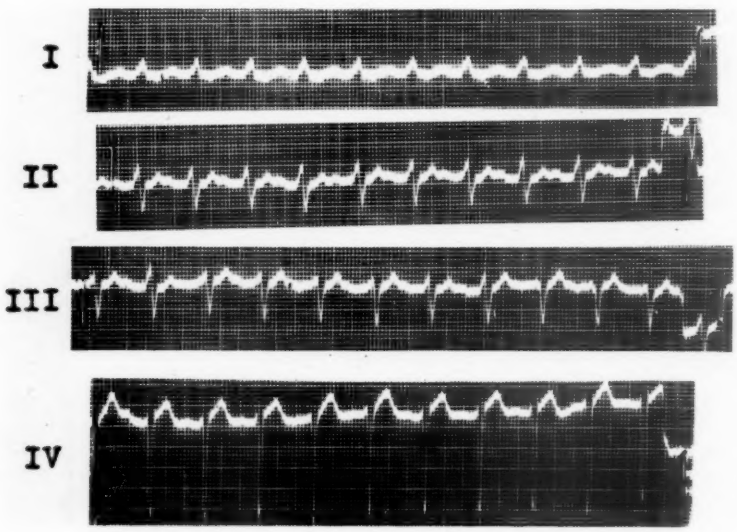


**Fig. 1.—Electrocardiogram. Sinus tachycardia, rate, 110 per minute. Prolonged auriculoventricular conduction. P-R interval, 0.24 second. QRS interval was 0.14 second and the configuration was that of typical left bundle branch block. The maximum height of the R wave in the chest lead (IV F) was 1 millimeter. Two other electrocardiograms taken showed no changes.**

The patient was digitalized and was given aminophylline and mercurial diuretics intravenously. Ammonium chloride and ephedrine were taken orally. He experienced an adequate diuresis and became less dyspneic but about a week after admission suffered severe attacks of asthma that were relieved by epinephrine, aminophylline, or ephedrine. He died suddenly on July 31, 1945, thirteen days after admission to the hospital.

The etiology of the cardiac disease was variously considered by different members of the clinical staff as rheumatic heart disease, congenital abnormality of the aortic valve, syphilitic aortitis, or calcific aortic stenosis with bacterial endocarditis.

*Autopsy.*—*

*Performed by I. I. L.

*Anatomical Summary:* The body was that of a well-developed, well-nourished white man, approximately 29 years of age, weighing 68 kilograms and measuring 175 cm. in length. There were semilunar areas of arcus senilis in both eyes.

Upon opening the thorax the heart was found to occupy a tremendous volume of thoracic space. The apex of the heart was found at the seventh intercostal space in the midaxillary line. The aortic arch as it leaves the heart was noted to be greatly widened. The heart weighed 900 grams. The pericardium was smooth and glistening. There was myocardial hypertrophy of the entire heart. The endocardium was smooth and glistening. On the aortic valve were found two verrucous-like vegetations approximately 1 mm. in diameter. No growth was evident on culture. However, on subculture an anaerobic strain of *Staphylococcus albus* was obtained. The valves measured as follows: mitral, 12.5 cm.; aortic, 12 cm.; pulmonic, 9 cm.; and tricuspid, 15 centimeters. The left ventricular wall was 19 mm. and the right, 6 mm. in thickness. The chambers of the heart were extremely dilated. The ascending portion of the aorta was tremendously enlarged into a bulging pouch which was 22 cm. in circumference. This continued for a distance of approximately 5.7 cm. superiorly, at which point the aorta abruptly narrowed down to a circumference of 5.8 centimeters. The intima of the dilated part of the aorta was wrinkled. The coronary arteries appeared to be grossly normal. The ostia, however, were somewhat occluded by a slight degree of distortion at their origin. The two arteries took origin in the normal place in regard to the aortic cusps but appeared to arise higher than usual. They were found 1.5 cm. above the edge of the aortic valve. The ostia were, however, patent. Fig. 2 shows

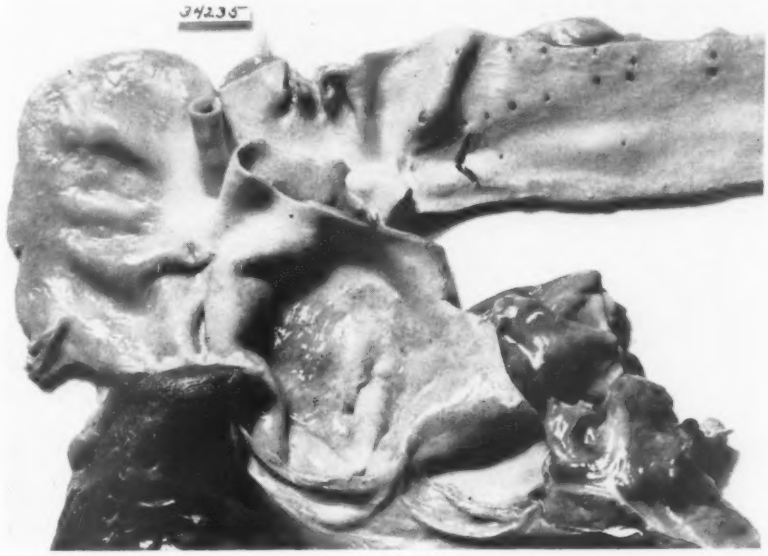


Fig. 2.—Detailed photograph of aorta. The aortic valve is tricuspid.

these changes. The interauricular septum was patent in the superior portion of the foramen ovale. This patency measured approximately 1.5 cm. in diameter. The chordae tendineae of the heart muscle were of normal size. The papillary muscles similarly appeared grossly normal. Several sections were taken from various places in the heart for microscopic study.

The pleurae were smooth and glistening. The right lung weighed 650 grams and the left, 640 grams. There was moderate chronic passive congestion. The pulmonary arteries were normal. There was approximately 150 c.c. of clear yellowish fluid in the right pleural cavity and 100 c.c. in the left pleural cavity. It was a transudate.

There was chronic passive congestion of all the viscera.

*Microscopic Findings:* The kidney, spleen, liver, and pancreas showed chronic passive congestion.

Sections from the lungs showed passive hyperemia. The lung capillaries were distended with red blood cells. The bronchial walls were thickened. There was no mucinous degeneration of the epithelium noted. The subepithelial tissue exhibited an increase in fibrous connective tissue. These same areas were infiltrated with round cells. There was evidence of extensive vascularity in the subepithelial connective tissue, as though chronic inflammatory change was present. The smooth muscle tissue was hypertrophied. Some of the bronchi contained an exudate consisting of fibrin, round cells, red blood cells, and an occasional eosinophil.

Papillary muscle of the heart showed considerable scarring. Some areas were fibrosed and there was revascularization. In the myocardium hypertrophy and small areas of interstitial fibrosis were seen.

## DISCUSSION OF PATHOLOGY

Serial sections were made of the aorta. The pulmonary artery exhibited no evidence of pathologic change. In and about the area of the aneurysm the most marked medial change was noted. The transverse and descending aorta were found to be grossly unchanged by any cystic medial necrosis, although even in these areas slight cystic medial degeneration was seen. The most marked changes were seen in the sections taken from the center of the aneurysmal dilatation just above its origin near the aortic valve. The hematoxylin and eosin stain

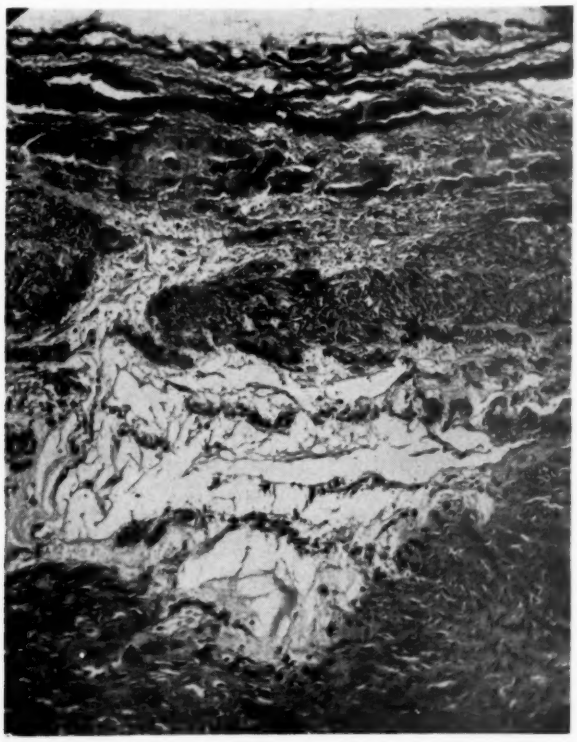

**Fig. 3.—Large cystic focus in media of ascending aorta. Hematoxylin and eosin; magnification × 125.**

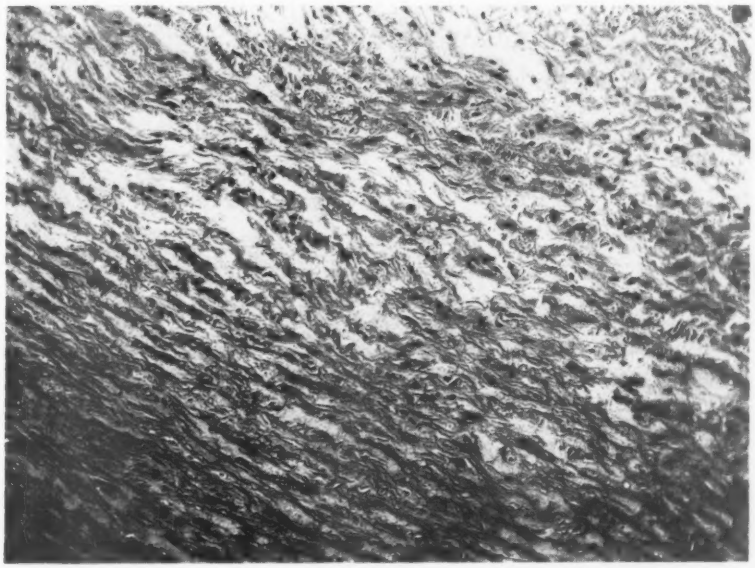

Fig. 4.—Cystic areas in media of ascending aorta. Polychrome methylene blue; magnification × 180.

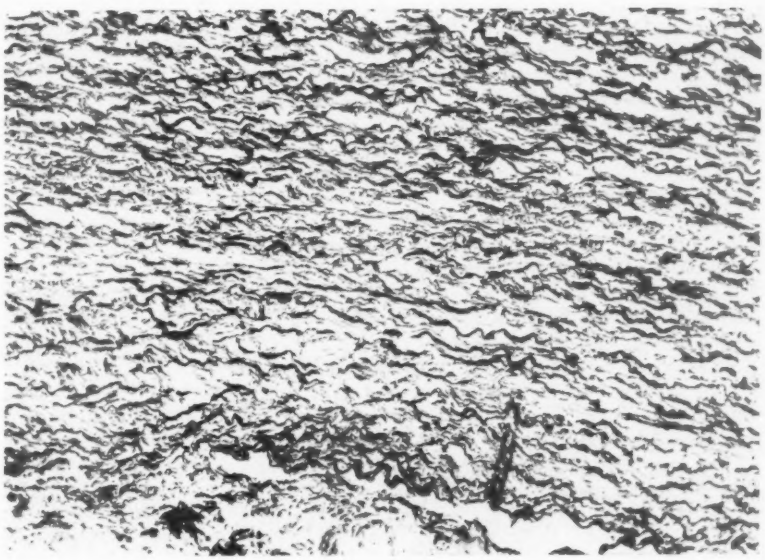

Fig. 5.—Fragmentation and displacement of the elastic fibers of the media. Orcein; magnification × 180.

showed several large cystic areas in the media, which are the characteristic lesions of the cystic medial necrosis originally described by Erdheim (Fig. 3). The polychrome methylene blue stain exhibited a marked color contrast in that the cystic areas stained a light pink color (Fig. 4). The orcein stain showed a marked displacement of the otherwise orderly elastic fibers (Fig. 5). Fat stain demonstrated small areas of free fat in and about the cystic area as well as in macrophages in the cystic area.

## SUMMARY AND CONCLUSIONS

A case of aneurysmal dilatation of the ascending aorta due to cystic medial necrosis of the aorta is presented. The gross appearance of these lesions is such that it may be confused with syphilitic aortitis if microscopic studies are not made. It is suggested that this diagnosis be considered in youthful patients with dilatation of the ascending aorta, aortic regurgitation, and associated congenital defects in the absence of syphilis, hypertension, and a rheumatic history.

Because of the not uncommon association of cystic medial necrosis of the aorta with other congenital defects, such as arachnodactyly and patent foramen ovale, and because of the similarity of the pathologic changes to those seen in some fetal blood vessels, it is our opinion that this lesion can be most likely explained on the basis of a congenital defect of the media of the aorta.

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# WOLFF-PARKINSON-WHITE SYNDROME PRESENTING CERTAIN UNUSUAL FEATURES

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THIS interesting disturbance of the cardiac conduction mechanism has received considerable comment in recent years. Some six patients presenting this abnormality have been seen in a regional station hospital in the past thirty months. The case report submitted is of a soldier in whom symptoms were more pronounced than in most of the cases described in the literature.

A white soldier, 22 years of age, was first seen at this hospital in September, 1943, when he was referred from the dispensary of his organization because of complaints of periodic attacks of rapid heart rate, dizziness, nausea, and precordial pain. The pain was sharp in character and was associated with the attacks of rapid heart action. He stated that he first noticed symptoms in 1940. An attack of rapid heart rate with dizziness had developed as he sawed wood on a farm in Midwestern United States. This persisted all day. This first attack had been followed by several similar attacks of shorter duration. He was unable to incriminate any particular activity as a cause but felt that many attacks were precipitated by sudden effort. Each attack began abruptly and ended similarly. Often he was conscious of a thumping sensation in the lower left chest as the attack ended. Lying down usually caused an attack to disappear. Once or twice during the attacks the legs had become swollen, but he had never developed a cough or produced any sputum during the attacks.

General physical examination on the occasion of this admission showed a robust individual weighing 175 pounds. No abnormalities of the skin were noted. There was no obvious dyspnea nor cyanosis. The lymph nodes were not enlarged. The lungs appeared normal. No definite enlargement of the heart was found on clinical examination nor were any significant irregularities of its action nor any important murmurs detected.

Routine urinalysis and blood count showed no abnormal findings. The blood Kahn reaction was negative.

A roentgenogram of the chest was considered normal. Chest fluoroscopy showed no enlargement of any of the chambers of the heart.

An electrocardiogram (Fig. 1) was considered to be normal.

After a few days of observation, the patient was returned to duty. During the hospital stay he exhibited no evidence of being dyspneic and no cardiac irregularity was detected.

Early in January, 1944, he was readmitted because of a papulomacular rash which had been first noted some two days after possible exposure to venereal disease. The eruption spread to involve the skin of the chest and abdomen. It was intensely itchy and was associated with a slight photophobia. The soldier was placed in an isolation ward and on the day following admission the eruption was replaced by a discrete pustular type of lesion developing in crops and suggesting chicken pox. Three days after admission a urethral discharge was noted which on culture was found to contain gonococci though the smears of the purulent discharge failed to show any such organisms. Treatment with sulfadiazine was instituted and the urethritis rapidly

Received for publication April 1, 1946.

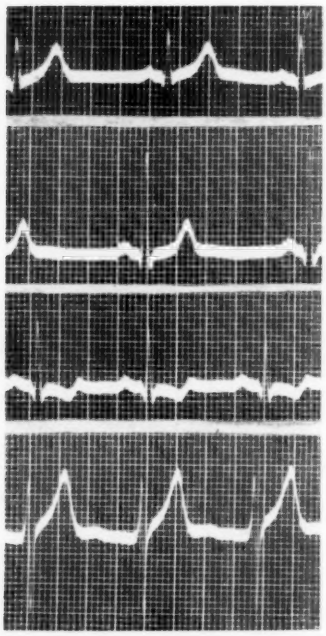

Fig. 1.—Electrocardiogram taken on Sept. 25, 1943.

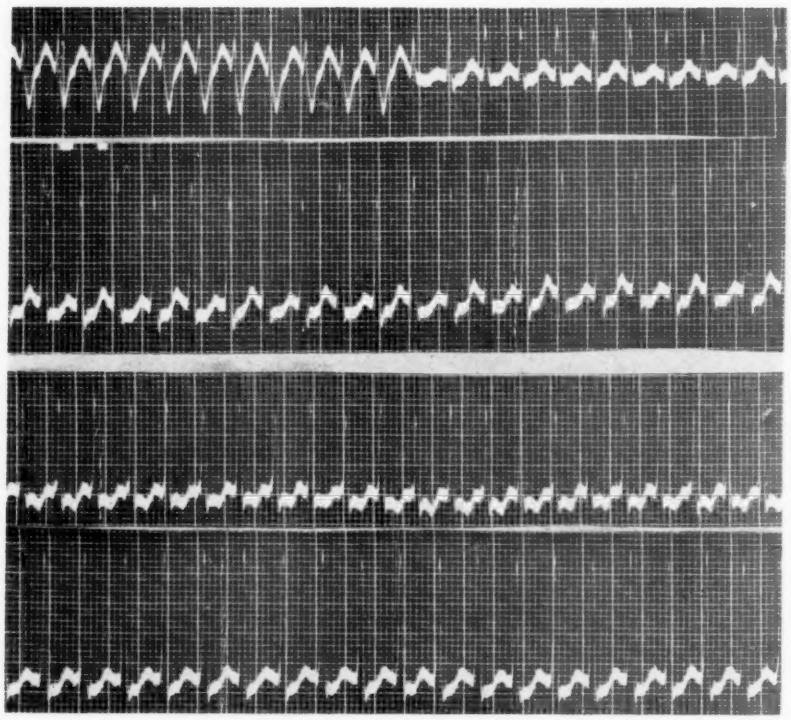

Fig. 2.—Electrocardiogram taken during an attack of paroxysmal tachycardia. Note the abrupt transition from one type of paroxysm to another.

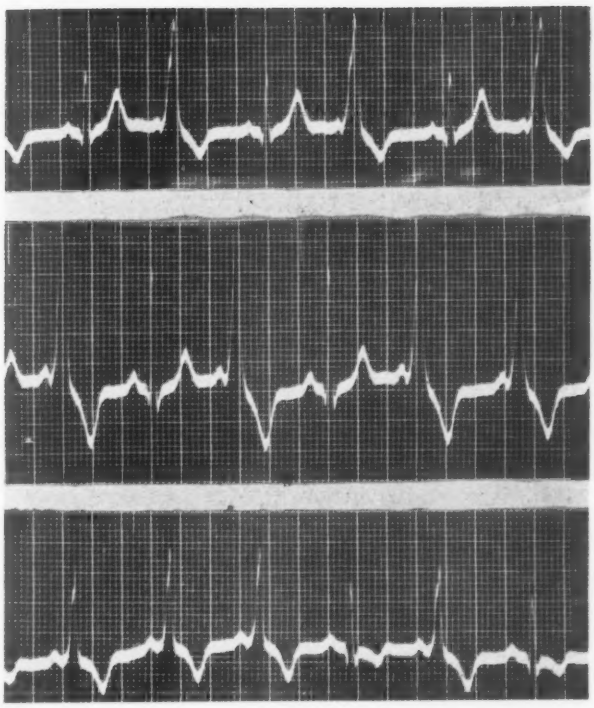

Fig. 3.—A normal complex alternating with abnormal complexes showing short P-R invervals with evident widening of the QRS complexes and inverted T waves. Only Leads I, II, and III are shown.

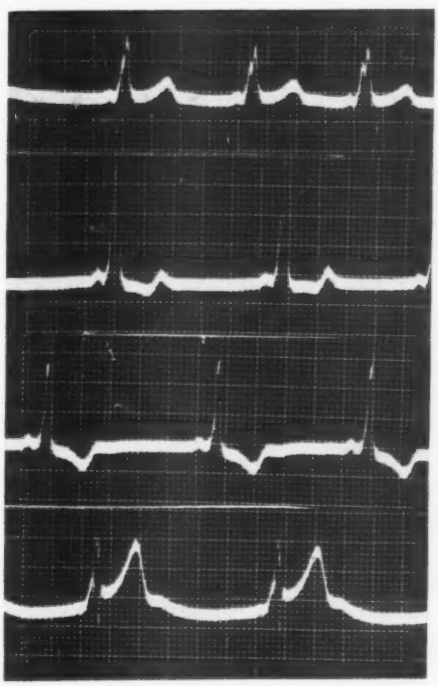

Fig. 4.—An electrocardiogram taken in December, 1942. The P-R interval is recorded as 0.08 second. The QRS duration is 0.14 second.

cleared. The skin rash disappeared within four days of admission. On Jan. 17, 1944, about 10:00 A.M., the patient suddenly developed an attack of weakness. It was noted that he was moderately dyspneic but not cyanotic. He did not cough. The radial pulse beat was rapid; a definite count could not be made. An electrocardiogram was taken immediately (Fig. 2). It showed a tachycardia which was apparently of two types. The first eleven complexes shown in Lead I conform to those seen in a ventricular tachycardia. This type of rhythm changed abruptly to a supraventricular rhythm of approximately the same rate. The latter suggested an A-V nodal type of paroxysmal tachycardia. From past experience, the soldier knew that by his lying supine in bed without moving the rapid rate would soon subside. Attempts to abort the attack by carotid pressure were without result. Within five minutes the rate suddenly slowed. This slowing was initiated by his noting a thumping sensation in the lower left chest. This occurred as the lead wires were being changed and is not recorded on the electrocardiogram. However, when the electrocardiogram was examined it was found that an apparently normal complex alternated with a complex presenting a short P-R interval (0.08 second), a widened QRS complex (0.12 second), and an inverted T wave in Leads I, II, and III (Fig. 3).

Further inquiry revealed that the patient had been subject to attacks of hay fever earlier in his life and had been given various types of medication for this. His first attack of tachycardia developed during an attack of sneezing. He had been told by a physician who had examined him sometime before he entered the Army that his electrocardiogram was abnormal. Because of this, shortly after his entry into the Military Service, he had been examined at an Army hospital. An electrocardiogram taken there in December, 1942, was requested and on examination was found to show a short P-R interval in all complexes, a widened QRS complex, with, however, an upright T wave in Lead I (Fig. 4).

Quinidine, 0.6 Gm. daily, was begun but seemed to have little effect. The electrocardiogram returned to normal; it was never apparent whether this occurred spontaneously or was a result of therapy. While at rest the soldier was comfortable, exhibiting no symptoms of illness. A cardiac murmur was not heard and at no time, clinically or by roentgenogram, could any cardiac enlargement be found.

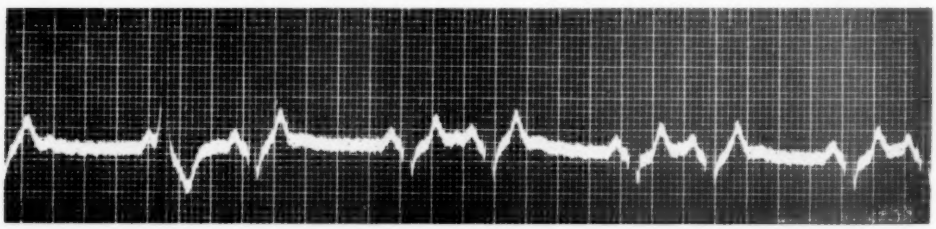

**Fig. 5.—Electrocardiogram showing a coupling of normal complexes with an occasional abnormal complex.**

The patient soon discovered that activity such as running a city block on smooth terrain resulted in the development of tachycardia. Usually this was supraventricular in type, but occasionally one or two widened complexes suggesting a ventricular tachycardia interjected themselves in the record. Occasionally, as is shown in Fig. 5, a peculiar coupling of normal complexes was demonstrated. This suggested a "sinus arrest." Resumption of a regular slow pulse rate always resulted from his lying supine for a few minutes and no other attempts at aborting an attack were considered. Epinephrine, 0.5 c.c. hypodermically, produced the same results as physical activity.

It became apparent that the soldier's disability was incapacitating and he was discharged from the Army.

The case which has been described presents the classical features of what has come to be known as the Wolff-Parkinson-White syndrome.[1] Commonly it is a source of little inconvenience to a patient unless the attacks of tachycardia are difficult to stop or last for long intervals. The widened QRS complexes of this syndrome must be sharply separated from the widened complexes of intraventricular or bundle branch block with their more ominous significance. Most cases described have shown a supraventricular type of tachycardia. In 1941, Levine and Beeson[2] described three cases and referred to the infrequency of occurrence of ventricular tachycardia in this condition.

## SUMMARY

A case of Wolff-Parkinson-White syndrome occurring in a young man is presented. It is felt the electrocardiographic findings which are described may serve to assist in the elucidation of some of the unsettled problems concerning the exact mechanism of this abnormality.

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# PULMONARY EDEMA IN THE PREGNANT PATIENT WITH MITRAL STENOSIS

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MEDICAL CORPS, ARMY OF THE UNITED STATES

INJUDICIOUS administration of intravenous fluids is a not uncommon cause of acute pulmonary edema. Patients with mitral stenosis are particularly susceptible to this hazard, especially during pregnancy. Two cases, recently under our care, clearly exemplify this danger.

## CASE REPORTS

CASE 1.—Mrs. E. M. T. H., a 29-year-old primigravida, was first seen in the prenatal clinic June 13, 1944. She gave a definite history of chorea and heart disease in childhood and stated that her father, a physician, had urged her to be careful of her heart. Routine examination however, was normal and the patient felt quite well throughout the pregnancy, having gained thirty-five pounds in weight. At no time did she experience any dyspnea, orthopnea, edema, or other evidence of limited cardiac reserve. Labor began Jan. 4, 1945, and was prolonged by a persistent occiput-posterior position and uterine inertia. After fifty-two hours of fairly hard labor, she was delivered by mid-forceps, under spinal anesthesia, with the use of Kjelland's forcepts for rotation. During this prolonged labor it was thought advisable to give the patient supplementary fluids. Accordingly, she received five separate intravenous infusions, each of 1,000 c.c. of 5 per cent glucose in saline, at twelve-hour intervals. The last of these infusions was given one hour before delivery. In the delivery room she received 1 unit (250 c.c.) of plasma before delivery and 500 c.c. of citrated blood afterward. She appeared well for the next ten hours, after which she complained of gradually increasing dyspnea.

Examination revealed slight cyanosis with difficult breathing. Râles were present throughout both lungs. The temperature was 99.2°F.; pulse, 100; and respirations, 28 per minute. The white cell count was 12,700. A clinical diagnosis of pneumonia was made and she was treated with penicillin, sulfadiazine, and oxygen for forty-eight hours without definite improvement. X-ray examination of the chest showed mottled infiltration of both lung fields, some fluid in the left costophrenic sinus, and enlargement of the heart. The radiologic interpretation was congestive heart failure. When seen by a medical consultant, a to-and-fro mitral murmur was heard at the apex. Moist râles were present throughout both lung fields. There was no enlargement of the liver, no noticeable distension of the neck or peripheral veins, and no demonstrable peripheral edema. Digitalis was prescribed, the fluid intake was restricted to 1,500 c.c. daily, and oxygen therapy was continued. The penicillin and sulfadiazine were discontinued.

From this time, improvement was rapid and at the end of sixty hours all clinical evidences of pulmonary edema had disappeared. The mitral systolic and diastolic murmurs gradually diminished in intensity so that two weeks later a rumbling mid-diastolic murmur could be elicited only by careful auscultation. X-ray examination showed normal lung fields and an essentially normal cardiac silhouette. Six weeks after delivery no murmurs at all could be elicited. She has remained well sine.

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Received for publication March 19, 1946.

*Summary.*—A young woman with "silent" mitral stenosis of long standing had never experienced any cardiac symptoms. Pulmonary edema developed ten hours after a long, hard labor, during which she received intravenous fluids.

CASE 2.—Mrs. J. H. H., a 27-year-old secundigravida, was first seen in the prenatal clinic in April, 1945, during the third month of pregnancy. She gave a history of chorea at 8 years of age with annual recurrences until she was 18 years old. She had never known of heart disease and six years previously had gone through a normal pregnancy without difficulty. Examination in the cardiac clinic disclosed a localized rumbling diastolic murmur at the apex. The clinical diagnosis of mitral stenosis was confirmed by x-ray examination which showed straightening of the left upper heart border in the postero-anterior view and pressure by the left auricle on the barium-filled esophagus in the left lateral view.

Her course was uneventful until July 4, 1945, when she was admitted to the hospital because of acute pyelonephritis. The night of admission she received 1,000 c.c. of 5 per cent glucose in saline without untoward effect. The next morning another infusion of 5 per cent glucose in saline was started. After fifteen minutes of moderately rapid flow, she suddenly developed severe dyspnea. On examination she was dyspneic and cyanotic and coughed frequently. There were numerous loud râles in both lungs. X-ray examination showed disseminated densities throughout both lung fields which suggested congestive failure. This emergency was treated promptly by the use of alternating tourniquets on all four extremities and by the administration of morphine, atropine, oxygen, and digitalis. Within three hours she was fairly comfortable so that the tourniquets were removed. Ten hours later she experienced a mild relapse. Again, rapid relief was obtained by the use of the tourniquets. There were no further recurrences of pulmonary edema and the next day she felt perfectly comfortable. At the end of two weeks she was allowed out of bed for short periods and three weeks later was delivered by classical cesarean section under local anesthesia without untoward effects.

*Summary.*—A young woman in the eighth month of pregnancy, with classical manifestations of mitral stenosis, but who had never been in failure nor had experienced any limitation of activities, suddenly developed acute pulmonary edema in the course of an intravenous infusion of 5 per cent glucose in saline. She responded quickly to therapy and was delivered five weeks later by a classical cesarean section.

## DISCUSSION

The dynamic equilibrium in the pulmonary circulation of pregnant patients with mitral stenosis is easily upset. Both the physiologic hydremia of pregnancy and the mechanical obstruction by the narrowed mitral diaphragm tend to cause pulmonary engorgement. Intravenous fluids may thus lead to acute pulmonary edema more readily than in normal individuals.

It is suggested that special precautions be taken in such patients as to the route of administration, rate of flow, and total quantity of parenteral fluids. The two cases reported here emphasize the fact that good exercise tolerance and inconspicuous physical findings may give a false sense of security.

## SUMMARY

The occurrence of pulmonary edema, in association with pregnancy, in two young women with mitral stenosis is reported. Neither patient had had any previous cardiovascular symptoms. In both patients the pulmonary edema followed the parenteral administration of large amounts of fluid.

# CHRONIC FIBROPLASTIC MYOCARDITIS

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CLINICIANS and pathologists frequently encounter cases of cardiac hypertrophy, with or without fibrosis, in young people. These cases are often not associated with the usual causes of cardiac hypertrophy. Mahon[1] has reported two cases of idiopathic hypertrophy of the heart with endocardial fibrosis in young children. In both of them the heart showed marked hypertrophy and, microscopically, severe myocardial fibrosis. Cases of apparently the same condition have been reported in adults by Levy and Rousselot[2] and by Levy and von Glahn.[3]

Doane and Skversky[4] have described a case of massive cardiac hypertrophy in which there were no valvular lesions or other possible causes for enlargement. This was also associated with active fibroplastic proliferation in the myocardium. Reifenstein and Chidsey[5] have reported a case of cardiac hypertrophy of unknown cause in an 11-year-old school boy.

Engelhardt and Bruno[6] have reported cases of Fiedler's myocarditis with autopsy findings; one patient lived two years. They stated that the heart showed cardiac hypertrophy with marked fibroplastic changes in the myocardium.

Saphir[7] has reported an analysis of 240 cases of myocarditis from autopsy material comprising 5,626 cases. This list included cases of both acute and chronic myocarditis and the etiologies embraced subacute bacterial endocarditis, pyemia, rheumatic bronchopneumonia, lobar pneumonia, and isolated Fiedler's myocarditis. Others occurred in association with ulcerative colitis, carcinoma, bronchiectasis, tuberculosis, streptococcic pneumonia, meningococcic meningitis, acute glomerulonephritis, pyelitis, chronic glomerulonephritis, diphtheria, typhoid fever, and influenza. Reference was also made to myocardial changes in measles, mumps, whooping cough, variola, varicella, paratyphoid, and dysentery.

Candel and Wheelock[8] have reported eleven clinical cases in which they were able to make the diagnosis of acute nonspecific myocarditis by means of symptoms and electrocardiographic changes. The causes of myocarditis in these cases were considered to be tonsillar abscess, lobar pneumonia, primary atypical pneumonia, scarlet fever, gonococcal arthritis, infectious mononucleosis, and typhus fever. One case of acute diffuse myocarditis was discovered, at autopsy, to have been associated with acute suppurative tonsillitis.

Scherf and Boyd[9] have asserted that with the frequency of acute infectious diseases and miscellaneous infections, there are but few persons who, during a

Received for publication April 4, 1946.

lifetime, do not have inflammatory myocardial foci. Alterations in the electrocardiogram, asthenia, slight precordial discomfort, and breathlessness occurring shortly after acute infectious diseases should be considered as possible indications of myocarditis.

From the preceding it can be seen that acute myocarditis may follow, or be associated with, a wide variety of diseases of both acute and chronic nature. The cases of chronic myocarditis with cardiac hypertrophy and fibrosis of apparently unknown etiology could be ascribed to many acute or chronic infections that the individual may have had in early life.

Two cases of chronic fibroplastic myocarditis associated with cardiac hypertrophy are presented. The etiology is obscure but might be the result of some unrecognized acute infectious disease which the individuals suffered earlier in life.

## CASE REPORTS

CASE 1.—A young woman, 23 years of age, was observed at intervals for seven years before her death. At the time of the initial examination, at the age of 16 years, no history was obtained of rheumatic fever, chorea, pneumonia, typhoid, scarlet fever, diphtheria, or malaria. She had had measles, chicken pox, whooping cough, and occasional attacks of tonsillitis as a child. A year

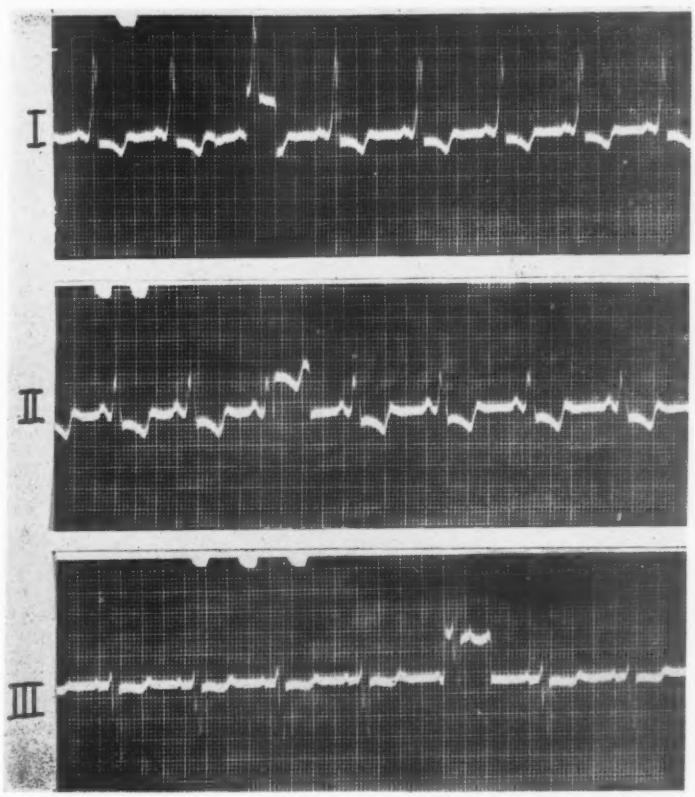


Fig. 1.—Case 1. Dec. 18, 1931.

before she was first seen by one of us (E. R. W.), a heart murmur had been discovered, but there was no history of cardiac symptoms. The family history was unimportant except for severe hypertension in her father. The only pertinent findings on physical examination were a blowing systolic murmur heard in the third and fourth left intercostal spaces close to the sternum, and less intensely at the apex, and an occasional premature contraction. By fluoroscopy, the heart was enlarged to the left without angulation of the left border; on rotation the cardiac shadow impinged on the aorta. No abnormalities were noted in the blood count, urine examination, or Wassermann test. The electrocardiogram showed left bundle branch block (Fig. 1).

The patient was observed frequently. There were no specific complaints or change in her status. Subsequent electrocardiograms showed little change from the original tracing. Shift of body position from the supine to the right and left lateral produced a variation in the height of the QRS complex in Lead I, suggesting no fixation of the heart by pericardial adhesions.

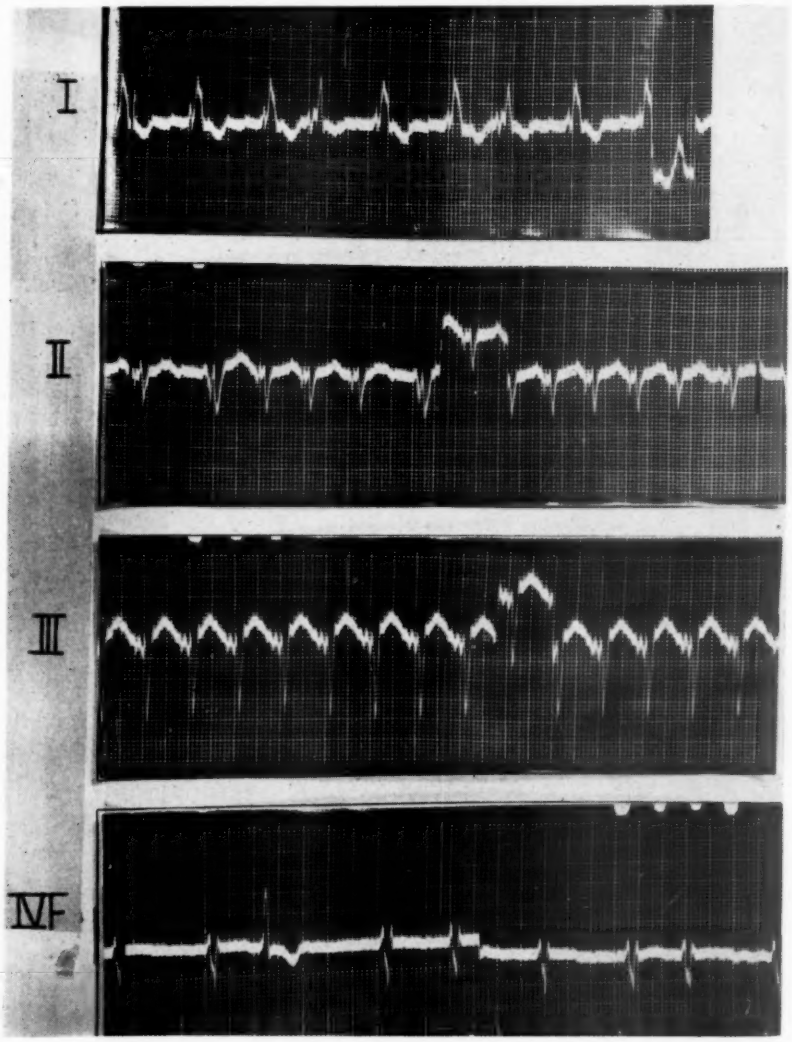


Fig. 2.—Case 1. May 3, 1938.

A month before death, a rapid and irregular heart rate developed, accompanied by moderate fatigue. For several weeks previously she had noted "occasional skips and misses" of the heartbeat and rare spells of tachycardia which had been terminated by right carotid pressure. On examination there were no objective signs of cardiac failure, but the heart rate was very rapid and totally irregular. The apex beat was in the fifth left intercostal space, 11 cm. from the midline. There was no thrill or murmur. The blood pressure ranged from 90 to 76 systolic; the

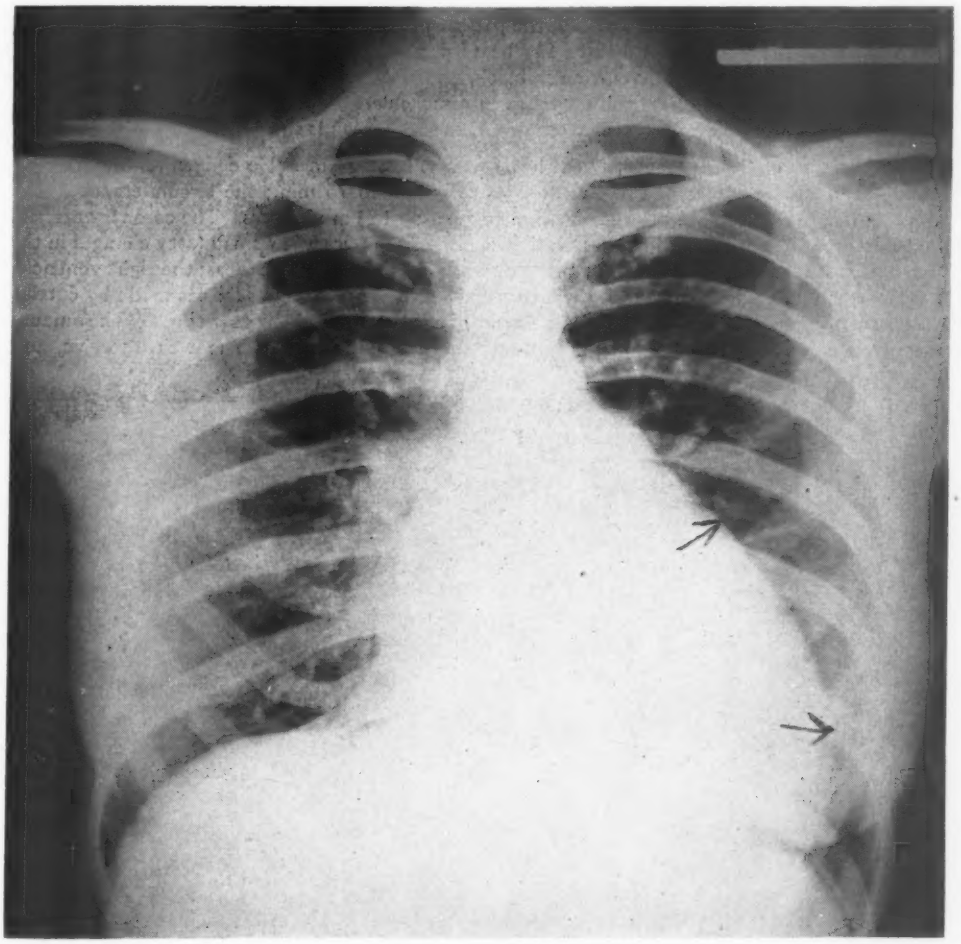

Fig. 3.—Case 1.

diastolic pressure was not obtained. The pulse was small and feeble. There was a considerable pulse deficit. No response was obtained by right or left carotid pressure. The electrocardiogram showed a pronounced change when compared with the tracing made seven years previously. The QRS complexes were wider and splintered and there was absence of $R_2$ and $R_3$ which were replaced by deep QS curves. The rhythm was impure flutter with a single premature ventricular contraction (Fig. 2).*

*In portions of the tracing (Fig. 2), pure flutter may be present. In Lead IV F, the mechanism suggests auricular fibrillation.

There was no response to 38 grains of quinidine which produced severe nausea and vomiting. Following digitalis intramuscularly, the heart rate promptly decreased and an electrocardiogram showed auricular fibrillation.

For two weeks the heart remained slow with a reversal to normal rhythm. No murmur could be detected. The second pulmonic was greater than the second aortic sound. The blood pressure was 92/78. X-ray films of the chest were reported to show cardiac enlargement, chiefly of the left ventricle and probably of the left auricle. The aorta was thought to be hypoplastic (Fig. 3).

Some days after leaving the hospital, the patient became acutely ill with severe dyspnea and a rapid, irregular heart rate of 135 to 140 beats per minute. The electrocardiogram showed sinoauricular tachycardia, intraventricular block, and frequent ventricular extrasystoles from a variety of foci. After morphine and digifoline intramuscularly, the heart rate fell to 100 and the patient believed the attack was terminated. Within a few seconds she very suddenly died.

*Necropsy Findings.*—At autopsy the heart weighed 450 grams. No congenital defects were found. The circumference of the pulmonic valve measured 75 mm.; the circumference of the tricuspid ring, 110 millimeters. The aortic valve measured 62 millimeters. The coronary arteries were patent, and the intima of the vessels was clear. There were a few small fatty changes in the arch and root of the aorta. The left ventricle measured 12 mm. in thickness; the right ventricle, 5 millimeters. The endocardium of the left ventricle was fibrous. On surfaces made by cutting the myocardium there was a marked replacement of the heart muscle by scar tissue. The amount of scar tissue in the ventricle and the septum was most remarkable. The arch, thoracic, and

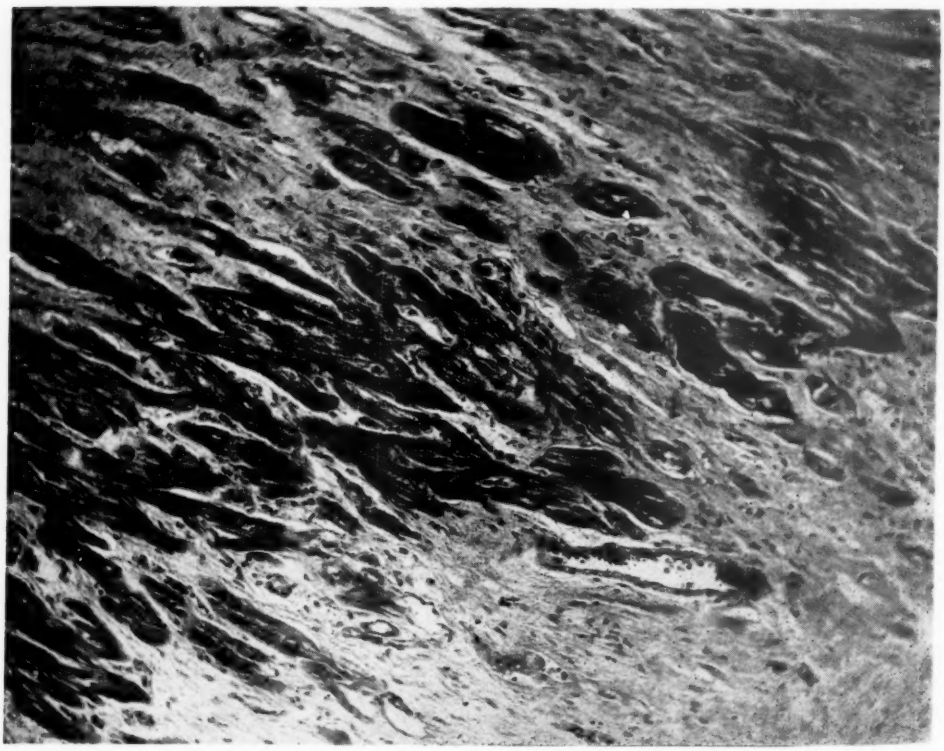

**Fig. 4.—Case 1. Section through heart muscle reveals muscle fibers replaced by dense hyalinized connective tissue. The muscle fibers that remain are enlarged and have lost their striations, and the nuclei are pycnotic. There is evidence of vascularization of fibrotic areas. (Hematoxylin and eosin, ×120.)**

abdominal portions of the aorta were negative. Microscopically the myocardium was markedly altered (Fig. 4). In many regions the muscle fibers were completely replaced by dense hyaline connective tissue which contained a few fibroblasts. The muscle fibers were pale, granular, and enlarged, and many of the nuclei were in various stages of degeneration. There was a generalized overgrowth of fibrous tissue in the septa separating the muscle bundles. In some places this increase was marked with corresponding atrophy of muscle tissue. There was a moderate infiltration of fat along the fibrous septa. There were no Aschoff bodies or specific inflammatory reactions in the sections studied. The fibrous tissue was most pronounced in the subendocardial areas. Much the same microscopic picture was seen in sections through the wall of both auricles. Culture of heart blood was negative.

A summary of the anatomic diagnosis was (1) marked chronic fibroplastic myocarditis; (2) chronic fibrous pericarditis; (3) hypertrophy of the myocardium of the right ventricle.

CASE 2.—A 23-year-old white woman was apparently perfectly well until two weeks before death, when she developed what she assumed was an ordinary cold. She remained at home in bed and on the following day was somewhat improved. Within the next two days, however, she developed an annoying cough, pain in the left side of the chest, and fever. Two days later a physician made a diagnosis of pneumonia. Following a few days of home treatment with no improvement, she was hospitalized.

On physical examination it was found that the patient was a pale young woman who seemed acutely ill and complained of cough and pains in the chest. The essential findings were confined to the lungs which showed impaired resonance over the left lower lobe with tubular breathing audible over the corresponding area which extended from the axillary region posteriorly to the left base. Over the right base there were also audible definite, coarse, moist râles but no change in the character of the breath sounds, aside from some exaggeration. A clinical diagnosis of lobar pneumonia of the left lower lobe and possible bronchopneumonia of the right lower lobe was made.

An x-ray film of the chest showed a homogeneous density in the left base, consistent with the diagnosis of pneumonia. Blood count showed a leucocytosis of 14,550 with 74 per cent polymorphonuclear cells. Sputum did not type for pneumococcus. Kahn test was negative.

The patient ran a septic temperature while in the hospital and was put on penicillin therapy, oxygen therapy, and glucose and saline intravenously. Her condition remained unchanged the first day, but then she became much worse with a drop in blood pressure to 70/52 and a pulse of 160 beats per minute. There were severe dyspnea and cyanosis. She was given supportive treatment for peripheral circulatory failure but with no response, and she died three days after admission in evident circulatory collapse.

*Necropsy Findings.*—At autopsy the heart weighed 545 grams. All of the chambers were markedly dilated. The left ventricular wall measured 23 millimeters. The circumference of the aortic ring measured 60 mm.; that of the pulmonary ring, 60 millimeters. The coronary arteries were smooth and patent but very small, measuring 3 to 5 mm. in circumference. The endocardium of the ventricles was everywhere fibrotic. The myocardium was firm and grayish-purple in color, and, on section through the wall of the ventricle and the interventricular septum, there were patchy areas of grayish-white which cut with increased resistance. Microscopic section of the myocardium (Fig. 5) revealed a diffuse patchy fibrosis throughout. In some areas, especially in the endocardium, this was more extensive than in others. The fibrous tissue was of a dense hyalinized type and relatively acellular. The muscle cells, which were not involved by the fibrosing process, were greatly hypertrophied and were somewhat granular. The nuclei appeared swollen and many of them were squared. The striations were diminished and many of the muscle cells were vacuolated and fragmented. There were various degrees of degeneration in the muscle cells; in some places this amounted to complete replacement by fibrous tissue. In some areas there were occasional round cell infiltrations. In others there were focal accumulations of plasma cells and round cells. None of these were typical Aschoff bodies. In none of the sections was

there any evidence of a recent inflammatory process. The epicardium was slightly thickened and fibrotic and moderately infiltrated with round cells. The lungs showed a severe bronchopneumonia and interstitial pneumonia.

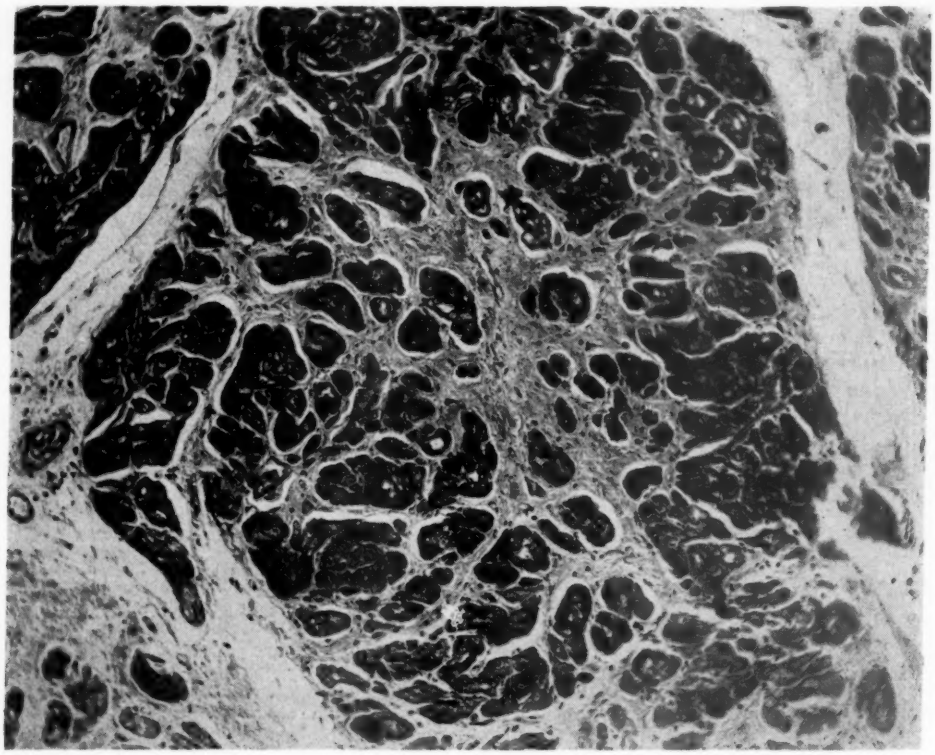

Fig. 5.—Case 2. Section through heart muscle reveals muscle bundles being replaced by dense hyalinized fibrous tissue. There is some round cell infiltration between the muscle bundles and into the fibrous tissue. The muscle fibers are enlarged and their nuclei are squared. The striations are barely visible, and some of the cells are vacuolated. (Hematoxylin and eosin, ×120.)

The anatomic diagnosis was (1) marked chronic fibroplastic myocarditis; (2) bronchopneumonia and interstitial pneumonia of the left lower, left upper, right lower, and middle lobes of the lungs.

## COMMENT

Two cases of chronic fibroplastic myocarditis associated with cardiac hypertrophy have been described. Both cases were in young women and the exact cause of the underlying pathology is obscure. In Case 1, the cause of death was the eventual failure of the diseased heart. In Case 2, death was caused by intercurrent pulmonary infection. The two hearts were practically identical, grossly and microscopically, and showed cardiac hypertrophy and fibrosis. We believe the distinctive pathology in these cases represents the healed end result of a previously existing acute myocarditis, or Fiedler's myocarditis, which may have been the result of some former acute illness.

## CONCLUSIONS

1. Two cases of chronic fibroplastic myocarditis associated with cardiac hypertrophy are presented. The etiology of the myocarditis is obscure but was probably associated with some acute infectious disease earlier in life.

2. A review of the literature reveals that myocardial involvement in the course of an acute infectious disease is more frequent than was formerly supposed and that careful evaluation and electrocardiographic investigation during the course of an acute infectious disease will reveal many more cases of cardiac involvement.

3. Numerous cases of chronic myocarditis have been reported in the literature in which the etiology can be traced to some acute or chronic infectious disease.

## ADDENDUM

Since the preparation of this article, Sellers and Phillips[10] have described two fatal cases of a similar nature in young individuals. They also suggest a like etiology for the diffuse myocardial fibrosis.

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# SINGLE CORONARY ARTERY

## Case Report of an Absent Right Coronary Artery

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ANOMALIES in size and distribution of the coronary arteries are fairly common but complete absence of one or the other of the main arteries is rare. In a study of the literature accompanying their report of a case, Krumbhaar and Ehrich[1] in 1938 found only five cases of absent right coronary artery that satisfied Hyrtle's postulate.[2] This postulate requires that one artery supply

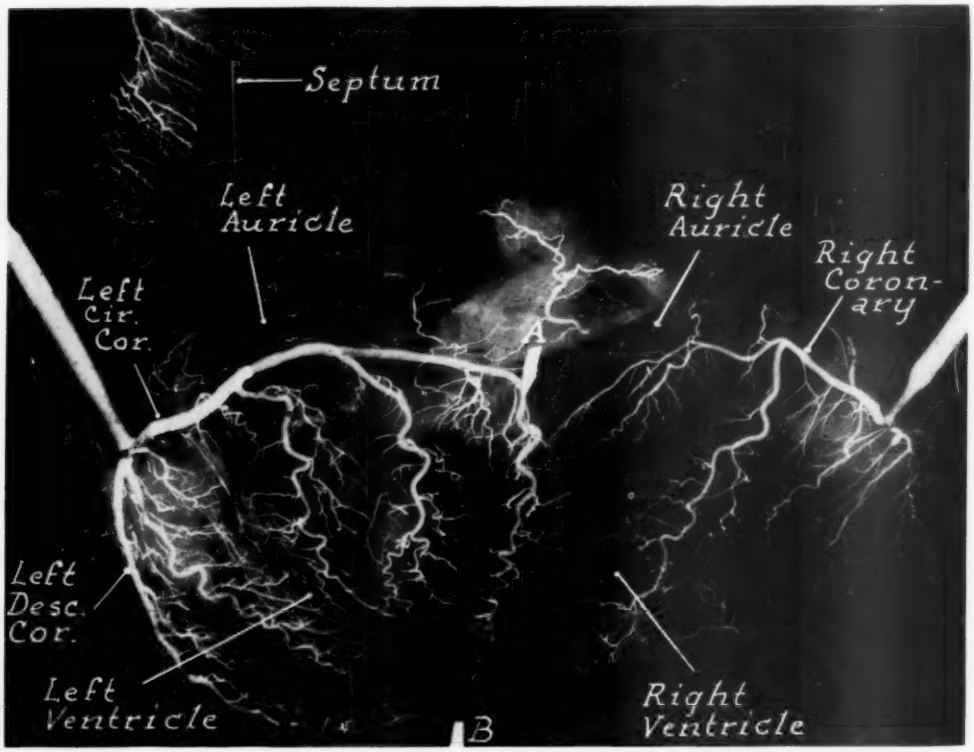


Fig. 1.—Roentgenogram of a normal arterial system following post-mortem injection. The specimen is opened and unrolled according to the Schlesinger technique[3] to bring the arteries into the same plane. *A* and *B* indicate the position of the posterior border of the interventricular septum which has been dissected out and placed in the upper right-hand corner. The posterior descending branch of the left circumflex is visible in the area between *A* and *B*.

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Received for publication April 10, 1946.

the whole heart and the anomaly must not be a matter of a common aortic orifice of the two arteries or an unusual origin of the missing one; that is, a misplaced anlage. Our purpose is to report another case of absent right coronary artery, the first in which a roentgenogram of the remaining coronary artery was obtained after its post-mortem injection with a radiopaque substance.

## CASE REPORT

A 66-year-old white woman was admitted to Colorado General Hospital on Aug. 24, 1942, complaining of severe abdominal pain, abdominal swelling, and vomiting of one month's duration. The past history was significant only for previous surgical removal of both Fallopian tubes and an ovary. Physical examination revealed abdominal tenderness, distention, and tympanitic resonance. The blood pressure was 160/90. A diagnosis of intestinal obstruction was made and the patient was treated by Wangensteen suction drainage, intravenous fluids, and supportive measures. Temporarily the response was good but after ten days, the abdominal distention recurred and laparotomy was performed on Sept. 4, 1942. Carcinomatous obstruction was discovered in the sigmoid region of the large intestine and cecostomy only was performed. The postoperative course was satisfactory until Sept. 18, 1942, when the patient suffered a sudden attack of dyspnea, loss of consciousness, and fall in blood pressure. Death occurred twenty minutes later.

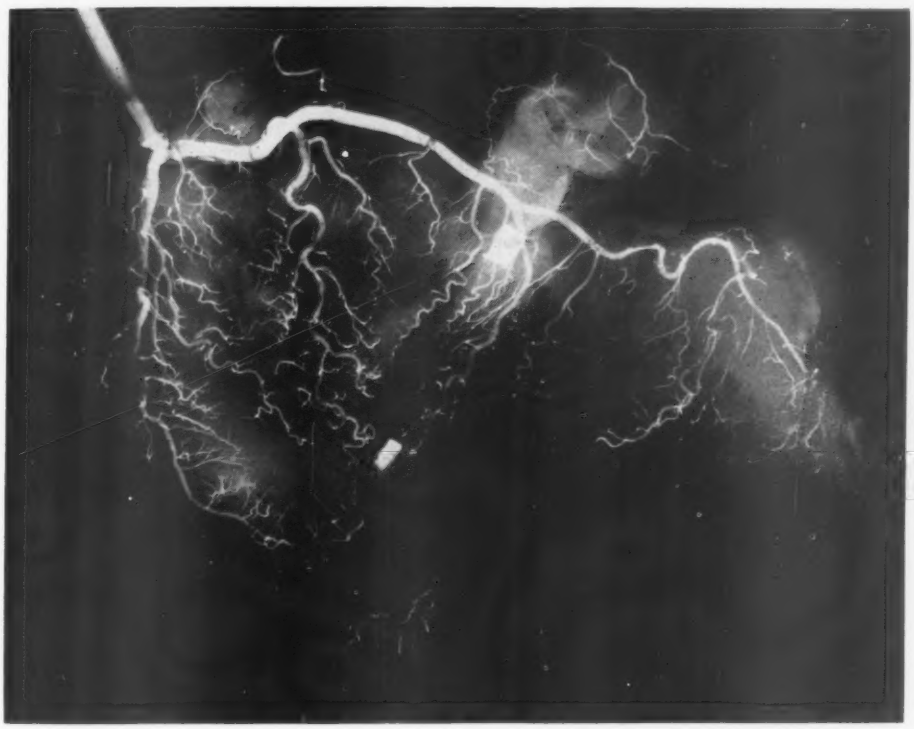

Fig. 2.—Roentgenogram of the arterial system with an absent right coronary artery. Note the continuation of the left circumflex artery beyond the posterior descending branch to supply all of the right ventricle. Interventricular septum below main specimen.

*Necropsy Report.*—The significant extracardiac findings were (1) an annular carcinoma in the sigmoid region of the large intestine with perforation and secondary pelvic abscess and (2) a large embolism involving the right pulmonary artery and its branches.

The heart weighed 340 grams. It was slightly enlarged but of normal shape and appearance. The tricuspid and mitral valves were slightly thickened along their free margins and the chordae tendineae and papillary muscles of the mitral valve were somewhat enlarged. The aortic valve showed a ringlike sclerosis of the bases of the cusps and, in addition, the posterior cusp was thickened by small calcified plaques. Microscopic examination of the heart revealed moderate to marked arteriosclerosis in vessels of all sizes. The largest arteries showed intimal thickening and infiltration by foam cells. In some fields the intima also showed crystalline deposits and calcification. Perivascular round-cell infiltration was present about the adventitial vasa vasorum. The medium- and small-sized arteries displayed intimal hyaline thickening and hyaline changes also in the other layers. The myocardium in both ventricles showed scattered areas of fibrosis in which atrophic myocardial fibers, round cells, fibroblasts, and pigment were apparent.

*Post-Mortem Injection and Roentgenography of Coronary Arteries.*—Only one coronary arterial orifice was found; it opened into the left anterior aortic sinus. This artery was injected and the specimen unrolled and radiographed according to the Schlesinger technique.[3] Fig. 1 shows the roentgenogram of a normal control with the coronary arteries and the various parts of the heart labelled. Fig. 2 is the roentgenogram of the case reported here. The right coronary artery was absent and its place and distribution were taken over by the circumflex branch of the left coronary artery. Instead of terminating in the posterior descending branch, as occurred in the normal in Fig. 1, the circumflex branch continued in the atrioventricular sulcus and supplied all of the right ventricle. Moderate distortion of the large arterial branches due to sclerosis was noted, but the lumens were not occluded at any point.

## SUMMARY

A case of absent right coronary artery is reported in which post-mortem injection and roentgenography of the coronary arteries were performed.

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# Abstracts and Reviews

## Selected Abstracts

**Mayock, R. L., Koop, C. E., Riegel, C., Kough, N. T., and Starr, I.: Convalescence from Surgical Procedures. III. The Relation of Nitrogen Balance and Blood Volume to Abnormalities of the Circulation.** Am. J. M. Sc. **212**:591 (Nov.), 1946.

The purpose of this investigation was to discover whether patients whose stores of nitrogen were maintained by special methods of feeding before or after operation were in reality in better condition than those who developed a negative nitrogen balance. The clinical impression of the surgeons that such was the case was confirmed by objective studies. Postoperative abnormalities noted in the ballistocardiogram occurred far more frequently in those in negative than in those in positive nitrogen balance, and the latter required a shorter average period of hospitalization than the former.

Interesting data were obtained concerning the relation of blood volume to the circulation, since a positive correlation existed between blood volume and cardiac output per minute. This is consistent with the view that the filling of the heart was improved by the increased amount of blood. Equally interesting was the relation between blood volume and abnormal ballistocardiograms, for the most abnormal types of ballistocardiograms occurred most frequently in patients with unusually small blood volumes. Poor cardiac filling may be responsible for these abnormalities since it has been shown that in some patients with obvious heart disease the abnormalities of form occur only in that part of the respiratory cycle in which cardiac filling is the poorest. Patients with biliary tract disease showed a pronounced tendency to have subnormal circulations before operation and to develop abnormal ballistocardiograms after operation.

DURANT.

**Priest, W. S., and McGee, C. S.: Streptomycin in the Treatment of Subacute Bacterial Endocarditis.** J. A. M. A. **132**:124 (Sept.), 1946.

In the treatment of subacute bacterial endocarditis with penicillin, four organisms were encountered by these authors which were highly or completely resistant to penicillin. One of these was the *Hemophilus parainfluenzae*; the other three organisms were strains of streptococci. The *Hemophilus parainfluenzae* was apparently unaffected after many weeks of penicillin therapy in daily dosage up to 2 million units. Sulfamerazine alone also had no apparent effect in vivo. Cure resulted from the combined administration of penicillin in daily dosage of 500,000 to 1,000,000 units and sulfamerzine in dosage to raise the level of the drug in the blood to 0.8 to 11 mg. per cubic centimeter. The organism in this case was subsequently found to be sensitive in vitro to streptomycin.

In a group of thirty-four patients, three strains of streptococci were encountered which were highly insensitive to penicillin. One was typically *Streptococcus viridans* after freezing, but was rather atypical in primary cultures of blood. The other two were typical nonhemolytic streptococci. The vitro sensitivity to penicillin ranged from 0.8 to 6 units per cubic centimeter. Sensitivity to streptomycin ranged from 0.1 to 1 unit per cubic centimeter. Streptomycin

apparently produced sterilization of the valvular lesions in Case 1, resulted in negative cultures of blood after penicillin therapy had failed in Case 2, and was solely responsible for the cure obtained in Case 3.

The dose of streptomycin used, 500,000 units (0.5 Gm.) per day, is not necessarily that which will be adequate in all cases in which the use of the drug is indicated.

BELLET.

**Ramos, G. J., and Peralta, R.: Effects of Quinidine on the Circulatory System.** Arch. Cardiol. Mex. **16**:302 (July), 1946.

The effect of small doses of quinidine on cats under dial anesthesia was studied. The heart rate, electrocardiogram, blood pressure, cardiac and vascular responses to central stimulation of the vagus and of the sciatic nerves, to temporary closure of both carotid arteries, and to epinephrine were investigated.

The effects of small doses of quinidine (0.25 mg. to 1.0 mg. per kilogram) were as follows: (1) The speed of recovery of the conducting system was decreased; this was shown by prolongation of the P-R interval whenever tachycardia was present. (2) The excitability of the myocardium was decreased in response to electrical stimulation or epinephrine injection. (3) The heart rate was decreased. Larger doses (1 to 5 mg. per kilogram) yielded similar but far more striking results: Prolongation of the P-R interval, even with a normal heart rate, decreased response of the heart to epinephrine, and to stimulation of the vagus nerve. Still larger doses (5 to 10 mg. per kilogram) resulted in a reduction of the blood pressure and a depression of the respiratory center.

LUISADA.

**Levine, H. D., and Erlanger, H.: Atabrine and the Electrocardiogram.** Am.J.M.Sc. **212**:538 (Nov.), 1946.

In a series of 179 individuals, atabrine in therapeutic and suppressive doses had no significant effect on the electrocardiogram. It is concluded that abnormalities previously reported as occurring in patients taking atabrine can be attributed to other causes.

DURANT.

**Patek, A. J., Jr., Kendall, F. E., Victor, J., Lowell, A., Colcher, H., and Seegal, D.: Venous Thrombosis After Infusion With Gelatin Solutions Containing Mercurial Preservatives.** Am.J.M.Sc. **212**:561 (Nov.), 1946.

Gelatin solutions containing phenyl mercuric borate or merthiolate as preservatives were injected eighty times into thirty-nine patients, usually in amounts of 1,000 cubic centimeters. Local thrombosis occurred in twenty-seven of the eighty veins injected. Venous thrombosis did not occur, however, when gelatin solutions free of mercurial preservatives were injected. Similar results were obtained in experimental studies using ear veins of rabbits. The addition of sodium thiosulfate or methionine to gelatin solutions containing phenyl mercuric borate appeared to give partial protection against the thrombotic action of this mercurial preservative. It is postulated that this converts the mercuric ions to the mercurous form and in this way renders the compound less irritative to the vein.

DURANT.

**Stein, I.: Postural Heart Block.** Am.J.M.Sc. **212**:604 (Nov.), 1946.

Two cases of alteration in the A-V conduction time resulting from change in posture are described. In one of these, complete heart block was present in the recumbent position, but lesser degrees of block were present when the patient was upright. The other patient presented a second degree heart block while supine and a first degree in the standing position. The block was caused by digitalis. Because both patients showed reduction of the block in response to atropine, vagal

action was assumed to be responsible for the findings. It is recommended that all patients with A-V conduction disturbances be studied in several postures for more complete evaluation of the clinical and electrocardiographic pictures.

DURANT.

**Taquini, A. C., and Lozada, B. B.: The Clinical Diagnosis of Tricuspid Valvular Lesions.** Medicina **6**:561, 1946.

An analysis of the symptoms and signs observed in fifteen patients with tricuspid valvular lesions led to the following conclusions: Dyspnea was the primary symptom in 14 patients, and appeared many years prior to other symptoms or signs of circulatory insufficiency. The color of the skin was normal in only one of the fifteen patients; eight had cyanosis and six of these were also slightly jaundiced. Venous congestion was present in every patient of the series. The venous pulse was the most significant diagnostic factor. Liver pulsation and a "balanced" thoracic movement were detected in thirteen instances. Twelve patients showed edema at some time: nine of these were ascitic, and three had hydrothorax. The auscultatory signs were not of great diagnostic value. The diagnosis could in many instances be confirmed by x-ray; the most significant findings in fluoroscopy and kymography were the positive systolic beating of the right auricle and vena cava, and the systolic elevation of the right hemidiaphragm.

MALINOW.

**Horrax, G.: Experiences With Cortical Excisions for the Relief of Intractable Pain in the Extremities.** Surgery **20**:593 (Nov.), 1946.

The results following excision of postcentral cortex for the relief of painful extremities in four patients are presented. In the two patients with causalgia and phantom limb pain, the cortical excisions were followed by transient relief only. In the two patients who had central pain, relief was complete in one during the remainder of his life (ten months); in the other, relief had been complete in the contralateral leg (one year and ten weeks, postoperatively) and was complete in the hand and arm for five months following the excision. Certain features concerned with sensory responses to cortical stimulation and sensory deficits following postcentral cortical excisions are discussed.

NAIDE.

**Elkin, D. C., and Harris, M. H.: Arteriovenous Aneurysm of the Vertebral Vessels.** Ann. Surg. **124**:934 (Nov.), 1946.

Of 500 operations performed for arteriovenous fistulae and aneurysms, ten were on arteriovenous fistulae of the vertebral vessels in their cervical or extracranial course. These ten cases are reported in detail with a review of the anatomy of the vessels, the diagnosis of the lesion and with suggested operative methods of approach and treatment.

Of all the aneurysms and fistulae in the body, the diagnosis of those of the vertebral vessels is the most difficult to make. It was made with certainty in only five patients in this series, although it was suspected in others. It is likely to be confused with more common lesions in this region, particularly fistulae between the internal jugular vein and branches of the external carotid artery. It may also be confused with fistulae arising from other branches of the subclavian artery, particulary the inferior thyroid, the transverse scapular and transverse cervical vessels. Since the common carotid lies moderately superficial in the neck where it can be occluded by digital pressure, the bruit of fistulae arising from branches of this vessel are usually obliterated with ease. If the bruit does not disappear on compression of the common carotic artery, the vertebral vessels should be suspected as the site of the lesion. Since the vertebral vessels lie deep in the neck, obliteration of the bruit is difficult to obtain by pressure.

NAIDE.

**Mangun, G., and Myers, V. C.: Cardiac Muscle: Further Studies: Investigation of Chemical Changes in Myocardial Insufficiency With Special Reference to Adenosinetriphosphate.** Arch. Int. Med. **78**:441 (Oct.), 1946.

The authors found that creatine, total phosphorus, acid soluble phosphosus, and potassium are decreased consistently in chemical studies of the muscle of the failing heart. One of the authors found also that in the late stages of cardiac failure in dogs with aortic insufficiency there was a marked decrease in the adenosinetriphosphate and phosphorus content of the left ventricle. In order to study this phenomenon in the human heart, the authors devised a technique compatible with the fact that adenosinetriphosphate and related compounds break down rapidly after death. The method consisted essentially in the precipitation of purines in hydrolized trichloroacetic acid extract of tissue with copper bisulfite and the estimation of the nitrogen content of the precipitate and conversion of unchanged adenosinetriphosphate purines to oxypurines. The left ventricle, right ventricle, and skeletal muscle of twenty-four specimens were examined at autopsy. Of the twenty-four patients, six had died of cardiac failure, five of tuberculosis, eight of pneumonia, and five of miscellaneous conditions. The results showed that the acid-extractable purine content of the left ventricle calculated as adenine is decreased in myocardial insufficiency. Lower concentrations of purine were also observed in the myocardium of the right ventricle in some but not all cases of pneumonia.

HORWITZ

**Cooper, W. M.: Clinical Evaluation of Sotradecol, A Sodium Alkyl Sulfate Solution, In The Injection Therapy Of Varicose Veins.** Surg., Gynec. & Obst. **83**:647 (Nov.), 1946.

The sclerosing therapy of varices has its limitations. One reason why it has recently fallen in disrepute is that the agents used were not adequate and had to be used in ineffective doses to avoid grave sequelae. The author reports the use of sodium tetradecyl sulfate solutions on 327 patients who received 2,064 injections in varicose veins with and without ligation of the saphenous vein and its tributaries. The experience with this sclerosing agent indicates that a substantial improvement of sclerosing therapy has been made possible with this new agent. It was found to be two to four times more effective than soap solutions. Its action appeared to be stronger and less diffuse. Side effects such as pain, cramps, sloughing, skin eruptions, and systemic reactions occurred much less frequently than with other sclerosing agents. The pharmacology of this compound is discussed and compared with agents used previously.

NAIDE.

**Wybauw, M.: The Amount of Vitamin $B_1$ In The Urine of Cardiovascular Patients Who Do Not Present a Frank Syndrome of Avitaminosis or of Hypovitaminosis But Are Nevertheless Clinically Improved by the Administration of This Vitamin ($B_1$).** Acta Cardiologica **1**:18, 1946.

The author studied a series of cardiac patients who showed no evidence of avitaminosis but were nevertheless improved symptomatically by administration of vitamin $B_1$. A dose of 2 mg. of vitamin $B_1$ was given to each patient. It was found that 16 to 29 per cent of the absorbed dose was excreted in the urine. This observation is regarded as further evidence that the improvement brought about by vitamin $B_1$ administration in cardiac patients is not contingent on the existence of avitaminosis.

LAPLACE.

**Goldblum, A., and Segall, H. N.: Progress Report on a Case of Auricular Fibrillation Demonstrated in an Infant of Three Months.** Canad. M. A. J. **55**:501 (Nov.), 1946.

In 1935 the authors made observations on a 3-month-old infant who had auricular fibrillation which probably had been present since birth. They were not able to find any report in the literature of a similar case. Neither quinidine nor digitalis therapy had any effect on the auricular rhythm which became normal spontaneously when the child was about 1 year old. The child

was next seen at the age of 9. A physical examination revealed essentially normal cardiac findings. The heart was normal in size and shape by roentgen study and the electrocardiogram was normal. Final examination was made in 1946 at the age of 11, at which time cardiac findings were also essentially normal.

BELLET.

**Quintin, T. J.: Complete Heart Block in Pregnancy (Report of Two Successful Deliveries).** Canad. M. A. J. **55**:600 (Dec.), 1946.

Quintin adds to the literature the report of another patient with complete heart block who satisfactorily withstood the strain of pregnancy and delivery. Up to 1938, Jensen had found only 14 such cases recorded in the literature. Most of the patients in whom complete heart block complicated pregnancy were delivered by cesarean section. In the patient reported by the author, two pregnancies were terminated by normal deliveries. The patient was 27 years of age during her first pregnancy and 29 years in her second. The electrocardiogram showed complete A-V heart block with a ventricular rate of 34 per minute. There was no evidence of cardiac embarrassment during pregnancy and the deliveries were uneventful.

BELLET.

**Selye, F. L.: The Absorption of Enteric Coated Ammonium Chloride.** Canad. M. A. J., **55**:45 (Nov.), 1946.

This author reports the not infrequent failure of enteric-coated tablets of ammonium chloride to be absorbed from the gastrointestinal tract. These may be observed as opaque particles by x-ray. In many instances in healthy young adults, prolonged administration of such tablets resulted in no acidosis, although the tablets were destroyed before excretion, presumably at a level too low in the gastrointestinal tract to allow absorption. He feels that the absorption of enteric-coated tablets is at best unpredictable. He later used ammonium chloride heavily coated with gelatin and observed gastric discomfort in only two of sixty cases; absorption occurred in all cases.

BELLET.

**Ochsner, A.: Venous Thrombosis.** J. A. M. A. **132**:827 (Dec. 7), 1946.

Clinical experience and experimental observation have shown that there are two types of venous thrombosis which differ etiologically, symptomatically, prognostically, and therapeutically. Thrombophlebitis consists of an inflammatory process associated with thrombosis, whereas phlebothrombosis may be defined as partial or complete venous occlusion by an intravascular clot which is unassociated with inflammation, the clot being loosely attached to the vein wall. In thrombophlebitis the femoral and iliac veins are usually the vessels involved. Since the thrombosis in thrombophlebitis is the result of inflammatory change in the vein wall, particularly the endothelium, the resulting clot is either a white or mixed thrombus and is firmly attached to the vein wall. For this reason, thrombophlebitis is, except in rare instances, not associated with embolism because the clot is attached and cannot become detached. In contrast, the mechanism of the formation of the thrombus in phlebothrombosis is entirely different. There is no inflammatory process in the vein wall and the clot is the result of two factors: the increased coagulability of the blood and the slowing of the blood stream. These thrombi usually originate in the veins of the calf muscles or in the veins of the plantar aspect of the foot, but may extend up into the deep veins of the thigh or pelvis. Because the clots are not firmly attached, portions of them frequently are carried through the venous system to the heart and lungs, and produce various grades of pulmonary infarction. It has been shown that 92 per cent of the patients with postoperative venous thrombosis and primary acute thrombophlebitis had hypercoagulability of the blood and that the average acceleration of blood coagulation in these patients was four and one-half times that in normal subjects.

In most cases of thrombophlebitis the clinical picture is definite and well defined. The patient complains of pain, fever and, usually, swelling of the extremity. Color changes and a lowering of the temperature of the extremity are often observed. In superficial vein involvement, the skin

overlying the affected vein is red and warm. The patient with phlebothrombosis is likely to have no symptoms whatever. This author is convinced that the diagnosis of phlebothrombosis must be made before any symptoms are manifest, because usually the symptoms are the result of a complication such as infarction or a beginning inflammatory process *resulting* from the retained thrombus. These patients do not usually have fever, but the erythrocyte sedimentation rate is usually increased and a positive Homan's sign should be looked for in all patients who are in bed and who have had tissue injury. This author believes that phlebography is unnecessary and that at the slightest sign of the condition immediate therapy should be instituted, before the clot has a chance to become detached.

The prognosis in thrombophlebitis as regards life is good, but unless adequate therapy is instituted, post-phlebitic sequelae, such as edema, pain, ulceration and streptococcic infection, are likely to develop. On the other hand, the patient with phlebothrombosis, although apparently not ill, is a potential fatality. The treatment of uncomplicated thrombophlebitis is conservative and consists of vasodilatation accomplished by anesthetizing the regional sympathetic ganglions. Only in rare cases of suppurative thrombophlebitis is radical therapy necessary; this consists of venous ligation proximal to the site of suppurative thrombophlebitis.

Phlebothrombosis, because of the great likelihood that the clot will become detached and produce pulmonary infarction or massive occlusion of the pulmonary artery which will cause sudden death, should be treated without delay by means of venous ligation or thrombectomy. Anticoagulant therapy may be used prophylactically in persons known to have a thrombosing tendency; in the treatment of phlebothrombosis it will prevent the formation of additional thrombi but will not prevent the detachment of the thrombus which already exists.

BELLET.

**Stein, I.: A Study of Abnormal T Waves in Patients Presenting no Evidence of Organic Heart Disease.** J. Lab. & Clin. Med. **31**:837 (Aug.), 1946.

Among 5,520 electrocardiograms made on 4,810 patients in the recumbent position at a large Army regional hospital, 51 or 1.0 per cent of this total showed evidences of abnormality of the T wave despite the absence of other criteria of heart disease. Bizarre T waves were confined to the chest leads in 23 of these, and in 28 they appeared in the limb leads. The subjects varied from 19 to 47 years and were of both sexes. The average age was 30, and the constitutional type varied widely between sthenic and the asthenic, the majority being, however, of medium build. A majority of the patients who showed this change in the T wave were psychoneurotic and presented symptoms referable to the cardiovascular system which could readily have been catalogued under the diagnosis of neurocirculatory asthenia. In 43 of 50 patients who showed the abnormal T wave, standard exercise tests converted the bizarre T wave to normal. The author discusses the possible underlying causes for the abnormality of the ventricular deflection and agrees with the conclusion of other writers that secondary imbalance of the autonomic nervous system is probably responsible for the changes.

WENDKOS.

**Schwartz, B. M., McIlroy, G. H., and Warren, H. A.: Acute Mediastinal Emphysema.** Ann. Int. Med., **25**:663, (Oct.), 1946.

Seven cases of acute mediastinal emphysema are discussed in some detail. The resemblance of some of the clinical features of this condition to angina pectoris, acute coronary thrombosis, and acute pericarditis are emphasized. In six of the cases, the etiology was not apparent; one was apparently caused by an acute respiratory infection associated with bronchial asthma. The mechanism responsible for acute mediastinal emphysema is briefly reviewed. The recurrent nature of the condition is stressed, in view of the experience with the seven cases reported in this paper. The association of pneumothorax is also emphasized and the authors indicate the desirability of making a careful examination of the precardial region for the physical signs of mediastinal emphysema in all cases with a small left apical pneumothorax. The most satisfactory treatment,

in their experience, consisted of prolonged bed rest. In all of the cases reported in this paper, the characteristic crackling sounds of mediastinal emphysema were heard, and for this reason the importance of this diagnostic sign is stressed by these authors.

WENDKOS.

**Andreyev, S. V., Borisova, E. I., and Rusinov, V. S.: Direct Electrocardiography of Heart During Restoration (Resuscitation of the Isolated Human Heart).** Am. Rev. Soviet Med. 4:4 (Oct.), 1946.

These authors recorded their observations on 100 isolated hearts obtained from children who had succumbed to various infections. The hearts were perfused with a modified oxygenated Tyrode solution. The experiments were started seven to thirty-six hours after death. In children up to 5 years of age the heart retains conductivity in situ up to thirty-six hours. Usually a series of premonitory signs are observed before normal contractility is resumed. These are: contraction of the aorta, response of the heart to mechanical stimulation, and fibrillation and flutter of the auricles. At the onset of revival, contractions of the cadaver heart are very weak, hardly noticeable, and the rate is slow, 20 to 25 per minute. There is no definite localization of the first foci of contraction, usually these foci are first observed in the right or left auricular appendage or in other parts of the auricles. With three or more foci of excitation, each governed by its own rhythm, the resulting graph of the composite action of the independent foci is a picture of fibrillation. When there are a total of five to six foci of contraction in both auricles, the resulting rhythm is auricular fibrillation with an auricular rate exceeding 300 per minute.

As a result of electrophysiologic observations on the cadaver heart during the restoration of its function, these authors conclude that fibrillation of the human heart is dependent on the appearance of a number of foci of excitation, each one of which initiates its independent rhythm.

In applying the lead electrodes directly to the right ventricle, the initial complex of the tracing has a small R wave directed upward without a preliminary Q wave and a long S wave directed downward. In applying the electrodes to the surface of the left ventricle, the R wave is preceded by a Q wave. They therefore obtain a graph identical with the initial complexes of partial electrocardiograms obtained separately from the right and left ventricles by Groedel.

They suggest that this method should prove valuable in the investigation of many other problems in electrocardiography.

BELLET.

**Hirsch, S.: Localized Amyloidosis Resembling Arteriosclerosis of the Heart,** Cardiologia 10:280, 1946.

The small branches of the coronary arteries, unlike the vessels of other organs, show no hyalinization or hyperplastic changes in arteriosclerosis. The author presents a 48-year-old white man with a negative history who died from a hepatoma of the liver. There were no clinical cardiovascular manifestations. At necropsy the heart weighted 265 grams and appeared entirely normal, except for a patch of atheroma in the left descending coronary artery. Histologically, the myocardium was normal. In the subepicardial tissue many small arteries and arterioles were found, rich in muscle fibers which showed deposits of amyloid localized to the media and occupying only parts of the circumference. In some vessels the lumen was almost obliterated. The color of this material was red-violet with hematoxyline-eosine. It gave the typical staining characteristics of amyloid. There were no changes in the endothelium and the adventitia and there were no inflammatory changes. In the area occupied by the amyloid, the nuclei, muscle fibers, and connective tissue were not recognizable. The author states that this lesion resembles hyaline arteriosclerosis. No trace of amyloid was found in the larger arteries, surrounding tissues, or in the rest of the body.

LENEL.

**Cohn-Czempin, R.: Cinnabane in the Treatment of Angina Pectoris,** Acta Med. Orient. **5:**292 (Sept.), 1946.

The favorable effect of Cinnabane, a benzyl-cinnamide, on otosclerosis, as reported by Seelenfreund, suggested the use of this new drug for the treatment of angina pectoris. In view of the vasodilator effect of the benzyl radical and its lipoid-solubility, the drug was expected to have a lasting rather than a transient effect.

The results of treatment of seventeen cases of angina pectoris are reported by this author. A course of treatment consisted of ten daily intramuscular injections of a 1 c.c. solution in oil. This treatment could be repeated once or twice after an interval of one week.

In fifteen of the seventeen patients cinnabane proved to be a powerful and lasting vasodilator. Pain usually disappeared after the first course. In the presence of hypertension, the blood pressure dropped gradually and remained low for a long time.

In seven patients, improvement of electrocardiographic findings were recorded. The improvement consisted in the disappearance of S-T segment depression and return to normal of inverted T waves in Lead IV F.

The author concludes that cinnabane, owing to its lasting action as vasodilator, has proved of great value in the treatment of angina pectoris, as well as other forms of heart disease caused by coronary insufficiency.

Another advantage is that cinnabane therapy can be given periodically, while other vasodilators must be taken continually in order to suppress pain and anginal attacks.

BELLET.

**Ben-Asher, S.: On the Toxicity of the Mercurial Diuretics: Observations on Eighteen Cases With Suggestions for the Prevention of Toxic Reaction.** Ann. Int. Med. **25:**711 (Oct.), 1946.

The author describes his experiences with 18 patients with congestive heart failure in whom the intravenous administration of a mercurial diuretic was followed by untoward symptoms, such as acute circulatory collapse or an acute cerebral episode manifested by delirium, drowsiness, or mental confusion. In 10 of the patients a delayed type of reaction occurred. Since nine of this number recovered after the administration of salt and water, the author ascribes the delayed reaction to excessive dehydration which resulted from the diuretic effect of the drug, superimposed on the excessive sweating which resulted from high environmental temperatures and humidity. An immediate untoward reaction occurred in eight other patients, but in seven of these, the repetition of such a reaction was prevented either by giving the drug slowly and intermittently or by preceding the injection with the intravenous administration of sodium thiosulphate. It is also the author's opinion that the occurrence of either type of reaction increased the seriousness of the prognosis; for this reason he strongly recommends a consideration of all factors which might prevent either form of reaction.

WENDKOS.

**Lequine, J., Segers, M., and Denolin, H.: Tachycardia Produced by Venous Hypertension in Man. A Study of the Bainbridge Reflex.** Acta Cardiologica **1:**1, 1946.

The mechanism of the Bainbridge reflex was studied in man by the following procedures: (1) increasing the venous pressure in a series of eleven normal subjects by the injection of one liter of physiologic serum, warmed to 37° C., into an arm vein in a period of five to ten minutes; (2) altering the venous pressure in a patient who had an arteriovenous fistula of the femoral vessels by intermittent compression of the fistula. During both procedures, records were made of the venous and arterial pressures and of the heart and respiratory rates.

The intravenous injections were followed by an increase in venous pressure of 5 to 74 mm. of water. The heart rate was accelerated by 8 to 25 per cent. In four subjects, 1.5 to 2.0 mg. of atropine was administered and during the resultant acceleration of the heart, the infusion was repeated. It was found that although the venous pressure increased as before, there was no appreciable increase of the heart rate. An exercise test after atropinization, on the other hand,

increased the heart rate by about 20 per cent. The possibility that an aortic reflex or increased respiratory movements were responsible for the cardiac acceleration during the infusion was excluded by the fact that the blood pressure change was very slight and that no significant change in respiratory rate was noted.

In the case of the arteriovenous fistula, closure of the fistula produced an initial increase of 30 mm. in the arterial pressure, but the pressure fell promptly to its original level in spite of the fistula remaining closed. The venous pressure, on the other hand, decreased to 25 mm. of water below its initial level and this hypotension persisted. The heart rate decreased from 100 to 60 beats per minute and then maintained a constant rate of 75. The association of the slower heart rate and lower venous pressure in the presence of a relatively unchanged arterial pressure was considered further evidence of the existence of the Bainbridge reflex. The administration of 1.5 mg. of atropine completely suppressed the response of the heart to compression of the fistula.

Acceleration of the respiratory rate by over 10 per cent occurred during the infusion of serum in eight of the eleven cases. On the other hand, altering the venous pressure by compressing and opening the fistula did not change the respiratory rate. When the venous pressure was elevated by infusion in the four subjects who received atropine, there was no increase in the respiratory rate. This respiratory reaction as it occurs in man is considered comparable to that described in the dog but is inconstant.

The Bainbridge reflex is concluded to be an important but partial element in determining exercise tachycardia.

LAPLACE.

**Goldfinger, D., and Wosika, P. H.: The Electrocardiographic Effects of Prostigmine.** Am.J.M.Sc. **212**:418 (Oct.), 1946.

The fact that tachycardia remains a difficult problem therapeutically and often interferes with the proper evaluation of the myocardial status through the interpretation of the electrocardiogram led the authors to study the effects of prostigmine. The study was felt to be especially indicated because of recent reports extolling the effect of this medication in all forms of tachycardia. The electrocardiographic changes were therefore observed in forty-two patients to whom 1 mg. of prostigmine methylsulfate was administered subcutaneously. The cardiac rate was slowed in 86 per cent of the patients studied. The series included patients with both organic and functional conditions. While this slowing may have been as little as 10 beats per minute in some instances, yet a similar result could not be obtained by any other method. Besides a decreased rate, other effects were noted, including transient inversion of the P wave, increase in amplitude of the QRS, increase in the amplitude of the T waves, separation of the fused T and P wave in auriculoventricular block, and slowing of the ventricular rate in auricular fibrillation and auricular flutter. Most of the effects upon the form of the electrocardiogram were explained upon the basis that the rate is slowed by stimulation of the parasympathetics. The P-R interval was uninfluenced except in one case of neurocirculatory asthenia in which it was shortened from 0.18 to 0.16 second and in one case of rheumatic heart disease in which it was lengthened from 0.16 to 0.18 second. The effect of the oral preparation of prostigmine bromide was disappointing when used therapeutically, notable slowing being achieved only with doses which produced intolerable side effects.

The procedure recommended in the study of the electrocardiogram is the comparison of the complete electrodardiogram before and twenty minutes after the injection.

DURANT.

**Breytspraak, R. W., and Greenspan, F. S.: The Effect of Aminophylline on the Prothrombin Time in Man.** Am.J.M.Sc. **212**:476 (Oct.), 1946.

Aminophylline was administered orally and intravenously, in full dosage, to a small series of young adult, male patients with mild bronchial asthma. The effects of the drug were studied with respect to the changes in the dilute (12.5 per cent) plasma prothrombin time. No significant

hyperprothrombinemia could be demonstrated in any of these cases. This is in contrast to previous observations, and would seem to indicate that fear of increased clotting tendencies suggested by these previous studies is unwarranted.

DURANT.

**Priest, W. S., Smith, J. M., and McGee, C. J.: The Effect of Anticoagulants on the Penicillin Therapy and the Pathologic Lesion of Subacute Bacterial Endocarditis.** New England J. Med. **235**:699 (Nov. 14), 1946.

Thirty-four patients with subacute bacterial endocarditis were treated with penicillin. Twelve of these received either heparin or dicumarol or both from the outset of penicillin therapy, three received anticoagulants with the penicillin only in the last of several courses of therapy, and nineteen were treated without anticoagulants. Difficulty was experienced in maintaining the desired coagulation time when heparin was administered, and in maintaining the desired prothrombin time after dicumarol. Considerable variation in individual response was observed with both drugs. In three patients, embolic phenomena disappeared after anticoagulants were given, but in five, embolism first appeared during their administration, and two additional patients suffered massive, fatal hemorrhages while receiving anticoagulants. This complication was not observed in any of the nineteen control cases. Of the fifteen patients to whom anticoagulants were given, eight died; whereas of the nineteen treated with penicillin alone only five died. However, the doses of penicillin given were not uniform, and the incidence of recovery was related to the size of daily penicillin dosage regardless of whether or not anticoagulants were given. Histologically no conclusive evidence in favor of anticoagulants could be demonstrated. The amount of fresh fibrin present on the valvular lesions was not demonstrably less than in untreated patients.

The authors conclude that no evidence was found that anticoagulants are a necessary adjunct to penicillin therapy in the treatment of subacute bacterial endocarditis.

KAY.

**Holman, E.: Roentgenologic Kymographic Studies of the Heart in the Presence of an Arteriovenous Fistula and Their Interpretation.** Ann. Surg. **124**:920 (Nov.), 1946.

Roentgenologic kymography provides important observations on the effect upon the heart and large vessels of closing a large arteriovenous fistula. The immediate effect is shown to be additional distention of an already dilated heart and aorta. This distention is due to backing up into the arterial bed of the blood formerly flowing through the fistula into the capacious venous bed. Since a large fistula of long duration is invariably accompanied by an increased total blood volume, the entire arterial bed, including the left heart and the aorta, is overdistended by this increased blood volume when the leak into the venous bed is suddenly closed. The immediate effect of such an overdistention of the arterial tree is a marked elevation of the systemic blood pressure, which is promptly though not completely rectified by a slowing of the cardiac contractions. This mechanism is dependent upon stimulation of the fibers of the depressor nerve in the arch of the aorta by the overdistention of this vessel which follows closure of the fistula and which is dependent upon the increase in total blood volume that occurs in the presence of a fistula of large size and long duration. The response is eliminated by atropinization of the patient and is therefore considered to be vagal in origin. If the fistula is closed permanently by operation, the blood pressure and heart rate return to normal through the gradual reduction of blood volume to normal. That the increase in blood volume and resulting circulatory effects occurs in all fistulas to greater or less degree seems likely, but these changes and effects are not always demonstrable by present instruments of precision or by present scientific methods in small fistulas with small increases in blood volume. In small fistulas also, these changes may be masked by other physiologic adjustments such as peripheral vasodilatation which may obviate the increase in general blood pressure when the blood volume increase is small.

NAIDE.

**Shumacker, H. B., Jr., and Carter, K. L.: Tests for Collateral Circulation in the Extremities.** Arch. Surg. **53**:359 (Oct.), 1946.

The determination of the adequacy of collateral circulation prior to exploration for aneurysm or arteriovenous fistula is most important. The authors feel that the most reliable and practical preoperative test for collateral circulation is the reactive hyperemia test. Though of great practical help and general reliability, this test is not infallible. The chief difficulties arise from the occasional impossibility of accurate compression of the involved arteries at the exact site of the fistula or aneurysm without concomittant compression of neighboring uninvolved vessels. If an excellent and complete flush occurs promptly during the test, with no further improvement on release of the compressed artery, one may approach the aneurysm and ligate, if necessary, the involved artery with minimal risk of ischemic difficulty.

If one does not succeed in establishing collateral circulation which is adequate according to this test, exploration should be carried out with great caution. The hand or foot should be exposed during operation and should be observed for change in color and temperature during prolonged temporary occlusion of the involved segment of artery. If ischemia of the hand or foot prevails, extirpation of the lesion should be deferred unless it is perfectly evident that a cure can be effected with maintenance of continuity of the involved artery. All preoperative study of collateral circulation is based on the premise that no collateral vessels will be needlessly destroyed during operation and that no postoperative thrombosis will occur.

NAIDE.

**Grand, M. J. H., Stanbury, J. B., Ekermeyer, E. W., and Purvis, J. D., Jr.: Rheumatic Fever: A Statistical Analysis of Incidence During Sulfadiazine Prophylaxis.** U. S. Nav. M. Bull. **46**:1793 (Dec.), 1946.

From December, 1943, to May, 1944, sulfadiazine was given to large groups of trainees at a naval training center as a prophylactic measure against streptococcal and other respiratory diseases. Specifically this drug was given to one regimental group, the complement of which ranged between four and five thousand men. Another regiment, whose complement ranged between two thousand five hundred and three thousand, received none of the drug and served as a control. There were eighteen cases of rheumatic fever in the treated group and twenty-six in the untreated group. Fifteen men developed rheumatic fever while still taking the drug; the other eleven became ill within four weeks after discontinuing prophylaxis. These figures are interpreted to indicate that in the group receiving sulfadiazine rheumatic fever was not eliminated but the number of cases was diminished.

BELLET.

**Blalock, A.: The Surgical Treatment of Congenital Pulmonic Stenosis.** Ann. Surg. **124**:879 (Nov.), 1946.

The results of the surgical treatment of congenital pulmonic stenosis in 110 patients are reported. The main indication for operation is evidence of an inadequate flow of blood to the lungs. Important in the diagnosis is the absence of visible pulsations in the lung fields as observed under the fluoroscope, and roentgenographic evidence that the pulmonary artery is small in size. The typical case of the "tetralogy of Fallot" should not present great difficulties in diagnosis. There are, however, many borderline cases in which it is difficult or impossible to be certain of the true nature of the condition. If, under such circumstances, the patient has a hopeless prognosis without an operation, an exploration is indicated.

The technique of the operation is described. The various arteries used for anastomosis to a pulmonary artery are the subclavian, innominate, and the common carotid. Of the 110 patients operated upon, twenty-five have died, with an over-all mortality rate of 23 per cent. An anastomosis was performed between the end of a systemic vessel and the side of one of the two pulmonary arteries in ninety-one of the one hundred ten patients. There were sixteen deaths in this group. The subclavian artery was used in forty-six patients with four deaths. One of these was due to hemoptysis on the fifth day which was believed to have been caused by the use of

dicumarol. The innominate artery was used in thirty-six patients; there were eleven deaths in this group. The commonest cause of death in this group was cerebral anemia or thrombosis. The end of the carotid was anastomosed to the side of one of the pulmonary arteries in nine patients. There was one death in this group which occurred nine months after operation. An end-to-end anastomosis was attempted between the end of a systemic artery and the end of one of the two pulmonary arteries in ten patients. This method was used because the pulmonary artery was very short or small, or because the patient was extremely ill and haste was necessary. There were four deaths in this series. Anastomosis was not performed in six patients. In four of these the pulmonary arterial pressure was high and it was thought that anastomosis was not indicated. These patients survived the exploratory operation. The remaining two patients died.

Severe bleeding from the anastomosis did not occur postoperatively in any case. There was no significant interference with the circulation of the arm on the side on which the subclavian artery was sacrified or used for the anastomosis in any of the patients. Weakness or paralysis of the opposite side of the body in patients in whom the innominate or carotid artery was used either had cleared up or was diminished in all who survived the operation. Although some of the operations were performed too recently to allow an evaluation, it appears that all of the patients, with one exception, who have survived the performance of an anastomosis are improved. Heart failure or *Streptococcus viridans* endarteritis has not developed thus far in any of the patients.

NAIDE.

**Master, A. M.: Effect of Injury and Effort on the Normal and the Diseased Heart.** New York State J. Med. **46**:2634 (Dec.), 1946.

This author discussed the relation of injury and effort to the onset of heart disease and to the production of exacerbations of symptoms in the presence of pre-existing heart damage. This subject is discussed particularly from the point of view of workmen's compensation.

The author believes that heart failure does not follow overexertion when the heart is normal. Effort probably never produces valvular damage if the valve is previously normal, although trauma in rare instances may cause rupture of a normal valve. A forceful impact of the chest wall against the heart results in damage to the heart muscle, usually in the form of hemorrhage; if the impact is severe, the heart and blood vessels may be ruptured. Trauma which is not so severe as to produce morphologic changes in the heart may produce disturbances in the heart function manifested chiefly by irregularities in rhythm. Contusion of the heart does not usually precipitate the classic type of coronary occlusion or thrombosis. Master is of the opinion that attacks of acute coronary occlusion are apparently unrelated to either exertion or occupation. Whether a causal relationship exists between effort and local hemorrhage or thrombosis in the brain has not been satisfactorily determined.

The presence of hypertension in association with dissecting aneurysm has led some authors to maintain that the dissection may be initiated by some unusual exertion or that effort causes rupture and fatal hemorrhage. No evidence was found to support the theory that elevated blood pressure is essential for the initiation of the dissecting aneurysm.

It is doubtful whether exertion or injury ever precipitates acute rheumatic fever. Trauma with resulting secondary infection may produce malignant endocarditis but not subacute bacterial endocarditis.

The author believes that severe trauma may produce rupture of an aortic aneurysm, but effort does not. When patients with narrowing of the coronary ostia due to syphilitic aortitis are subjected to effort, excitement, or similar stress, acute myomalacia without acute coronary occlusion may result.

A person with neurocirculatory asthenia cannot perform heavy physical work; his symptoms may be aggravated temporarily by accidents or effort. Arrhythmias may result from heavy work or unusual physical strain or following an accident.

Heart failure will not be observed in a normal man or woman as a result of unusual effort or trauma, but a diseased heart may fail under the stress of unusual effort or as a result of trauma.

BELLET.

**Freeman, N.: Arterial Repair in the Treatment of Aneurysms and Arteriovenous Fistulae.** Ann. Surg. **124**:888 (Nov.), 1946.

The incidence of gangrene due to acute ischemia following operations on aneurysms and arteriovenous fistulas is rare. Not a single instance occurred in 100 patients operated upon at the DeWitt General Hospital. There was but one case in the entire series of patients in the three Vascular Centers of the U. S. Army. This splendid record is probably due both to the policy of waiting a sufficient length of time for the development of collateral circulation and to the perfection of surgical technique designed to spare the important collaterals. In addition, prophylactic sympathectomy may have helped in practically abolishing gangrene after operations on arterial lesions.

Although there is sufficient circulation to care for the metabolic needs of the tissues at rest, interruption of the major artery to a limb may lead to persistent symptoms of impaired circulation such as intermittent claudication. Arterial repair was attempted in the treatment of twenty-three aneurysms and arteriovenous fistulae. Success was demonstrable either by arteriography or by the presence of normal peripheral arterial pulsations in eighteen of these attempts. In one case, recurrence of an arterial aneurysm was subsequently reported by the patient. In a second patient, recurrence of an arteriovenous fistula followed transvenous suture and subsequent excision of the lesion was necessary. Thrombosis at the suture line occurred in three of the twenty-three patients but the collateral circulation proved sufficient to prevent gangrene.

Repair of the defect in the wall of the vein was performed on 18 patients After the recovery of 12 of these patients, phlebography demonstrated the patency of the vein in six patients, but in six others postoperative studies showed the vein to be occluded. No instance of thrombophlebitis or pulmonary embolism was encountered.

Transverse suture of the defect in the arterial wall after excision of the damaged portion has been found more satisfactory than longitudinal suture, end-to-end anastomosis, or transvenous repair. Oscillometry has demonstrated marked improvement in the circulation in patients after repair of arterial lesions. The functional capacity, especially as shown by freedom from intermittent claudication, is increased in patients when the continuity of the major artery to the extremity is preserved.

NAIDE.

**Winton, S. S., and Wallace, L.: An Electrocardiographic Study of Psychoneurotic Patients.** Psychosom. Med. **8**:332 (Sept.-Oct.), 1946.

The authors analyzed the electrocardiographic records of seventy-six psychotic and neurotic patients, shown by physical examination and functional inquiry to be free of organic heart disease, in order to determine whether certain combinations of electrocardiographic changes could be found which formed any definite pattern characteristic of this type of patient.

Twelve per cent of these patients showed right ventricular hypertrophy; as seen by tall P waves, right axis deviation and RS-T segment depression in the limb leads. Deep S waves as an isolated abnormality occurred almost as frequently as in routine electrocardiograms of normal young individuals.

Flat or inverted T waves in Leads I and II occurred about fifteen times as frequently in psychoneurotic patients as in a large group of young healthy aviators. RS-T depressions of at least 0.5 mm. in Leads I and II were about six times as frequent as in normal individuals.

It was concluded that there is no combination of abnormalities which fits a distinct electrocardiographic pattern characteristic of this group of patients. BELLET.

**Wolf, G. A., and Wolff, H. G.: Studies on the Nature of Certain Symptoms Associated With Cardiovascular Disorders.** Psychosom. Med. **8**:293 (Sept.-Oct.), 1946.

These authors focused their study upon the reactions of a small group of individuals to a variety of life situations, with special reference to the effect of these situations upon cardiovascular and respiratory functions. Emphasis was placed upon the reactions to persistent low-grade stresses and strains which are a part of everyday living rather than upon the well-known responses

to the major crises of life. Attempts were made to ascertain to what extent efficiency of the cardiovascular and respiratory systems was impaired during certain life situations, what the identifiable emotional responses were, and how these various reactions bear upon symptoms and disease.

Statements in the literature concerning the effect of anxiety upon bodily functions are common. Unfortunately, such references focus attention upon the emotional aspects of the response to a situation rather than upon the effect of the situation upon the entire organism. It is the latter conflict which is important to the physician.

These studies revealed the following: dyspnea and palpitation, associated with inefficient pulmonary ventilation, may occur in response to stress-producing life situations which are associated with anxiety, anger, guilt, rage, frustration, and tension. Heart pain, in the presence of anatomical narrowing of the arteries, may result from a fall in the cardiac output and coronary blood flow in association with desperation and defeat. Stress-producing situations increase the work of the heart as shown by increases in blood pressure and cardiac output. The normal heart under strain is able usually to withstand this increased work without manifesting pain.

Giddiness and faintness may result from cerebral anoxia attendant upon diminished venous return to the heart. Giddiness and faintness may also result from hyperventilation which is followed by cerebral vasoconstriction, impaired dissociation of oxyhemoglobin, and cerebral anoxia. Cerebral anoxia may occur in response to stress-producing life situations in association with feelings of exhaustion, anxiety, fear, and during the early part of convalescence. Fatigue is a complex state which may be dependent upon emotional attitude, the absence of a dominant motivation, and the presence of a stress-producing life situation with accompanying inefficiency of cardiovascular and respiratory function. Individuals differ considerably as regards the intensity and duration of the cardiovascular and respiratory responses to life situations.

These results indicate that, in a setting of adverse life circumstances and associated emotional reactions, performance is costly, in terms of respiration and work of the heart. This high cost may manifest itself in cardiovascular symptoms which are not dependent alone upon gross structural disorder.

BELLET.

**Schroeder, E. F., Rose, F. A., and Most, H.: Effect of Antimony on the Electrocardiogram.** Am. J. M. Sc. **212**:697 (Dec.), 1946.

Trivalent and pentavalent antimony compounds have been used extensively in the treatment of human schistosomiasis and leishmaniasis and more recently to a limited degree in human filariasis. The major application of antimony as a therapeutic agent in the recent war has been its use in the treatment of *Schistosomiasis japonica*. Fuadin and tartar emetic are the drugs principally used in the treatment of this infection. Attempts have been made to explain sudden deaths which occasionally occur during such therapy on the basis of myocardial changes. The authors therefore have analyzed 315 electrocardiograms made on 100 patients during various stages of treatment with tartar emetic and fuadin for schistosomiasis infection. The changes noted included an increased amplitude of P waves in Leads II and III (found in 11 per cent of the patients), a fusion of the ST segment and T waves (found in 45 per cent), varying degrees of decrease in amplitude of the T waves (found in 99 per cent), and abnormal prolongation of the Q-T interval (found in 27 per cent). Deep inversion of the T waves occurred in many of the cases. The duration of these changes was variable; the changes were present up to two months after cessation of treatment. The etiology and significance of the changes remain unknown. It is the authors' opinion that these changes represent a transient side action of antimony and are not indicative of cardiac damage or serious impairment of cardiac function. They emphasize the fact that recent antimony therapy must be considered in evaluating abnormal electrocardiograms found in veterans and others.

DURANT.

**McPeak, E. M., and Levine, S. A.: The Preponderance of Right Hydrothorax in Congestive Heart Failure.** Ann. Int. Med. **25**:916 (Dec.), 1946.

The authors speculate upon the various mechanisms which might operate in congestive heart failure to localize pleural effusions in the right chest. Although no final conclusions are made, they suggest that exudation from visceral pleural capillaries secondary to anoxia in combination with impaired lymphatic drainage may be important contributory factors. The opinions expressed are based on an analysis of seventy-five cases requiring thoracentesis, fifty-two cases in whom effusion into the pleural cavity had been demonstrated by the roentgenologist but in whom thoracentesis had not been done, and an additional 110 cases in whom effusion into the pleural sac had been found at autopsy. In the first group, the effusion was limited to the right side in 75 per cent of the cases with rheumatic heart disease, and in 50 per cent of the cases with hypertensive and arteriosclerotic heart disease. In the second group, it occurred in one-half of the cases of rheumatic heart disease and in one-third of the cases of hypertensive and arteriosclerotic heart disease. In the third group, the effusion was only rarely limited to a single pleural cavity. Of those who at necropsy showed bilateral effusions, larger amounts were estimated to be present in the right chest in forty-four out of fifty-five cases of rheumatic heart disease and in thirty-six out of forty-eight cases of hypertensive and arteriosclerotic heart disease.

WENDKOS.

**Russek, H. I., Cutler, J. C., Fromer, S. A., and Zohman, B. L.: Treatment of Cardiovascular Syphilis With Penicillin.** Ann. Int. Med. **25**:957 (Dec.), 1946.

Fifteen consecutive cases of cardiovascular syphilis, including four with aortic aneurysm, were treated with penicillin in the dosage of 40,000 units every two hours for 85 doses. No significant untoward reactions which necessitated discontinuance of the drug were encountered. Four cases showed distinct improvement in coronary reserve following treatment. Electrocardiographic confirmation of such improvement was not obtained. In one instance, mild substernal pain recurred intermittently at rest on the third day of treatment, but disappeared after several hours without interruption of therapy. It is concluded that harmful reactions to penicillin are uncommon in cardiovascular syphilis during the treatment and early post-treatment periods, and that this form of therapy warrants further evaluation. WENDKOS.

**Gordon, L. Z., and Thurber, D. C.: Temporal Arteritis: Report of a Case and a Comparison With Respect to Periarteritis Nodosa.** Arch. Path. **42**:402 (Oct.), 1946.

The authors report a case of arteritis of the temporal artery occurring in a 65-year-old man who complained of severe headache, pain over both temporal regions, and severe pain in both thighs. These symptoms were accompanied by fatigue, anorexia, fever, anemia, and rapid sedimentation rate. Biopsy of the tender pulsating temporal arteries revealed active arteritis with epithelioid, lymphocytic, and granulomatous cellular infiltration throughout all the arterial coats. Multinucleated giant cells were present. The clinical findings indicated an infectious basis for the temporal arteritis; bacteriologic and serologic studies failed to reveal a bacteriologic factor.

The authors feel that the pain in the thighs was a part of the clinical picture, and that the disease known as temporal arteritis is in reality only a part of a widespread polyarteritis. They based their conclusion on a comparison of the findings in their case with reports of necropsy examinations in this disease, in which it was pointed out that many arteries exhibit the same pathologic changes as do the temporal vessels.

The writers find it difficult to differentiate this disease from periarteritis nodosa on the basis of cellular reaction. They believe that the histologic pictures are similar in both diseases. They point out, however, that periarteritis nodosa generally involves visceral arteries and less commonly the peripheral arteries; whereas temporal arteritis, only occasionally found in visceral arteries, is commonly present in the aorta, the innominate, carotid, subclavian, and iliac arteries as well as the temporal vessels. They also emphasize the fact that periarteritis nodosa is a fatal disease while in temporal arteritis the prognosis is generally good.

GAULEY.

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THE American Heart Association was founded in 1924 "for the study of and the dissemination and application of knowledge concerning the causes, treatment and prevention of heart disease; the gathering of information on heart disease; the development and application of measures that would prevent heart disease; seeking and provision of occupations suitable for heart disease patients; the promotion of the establishment of special dispensary classes for heart disease patients; the extension of opportunities for adequate care of cardiac convalescents; the promotion of permanent institutional care for such cardiac patients as are hopelessly incapacitated from self-support; and the encouragement and establishment of local associations with similar objects throughout the United States."

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning the circulation of blood and lymph. Any physician or investigator may become a member of the section after election to the American Heart Association and payment of dues to that organization.

The American Council on Rheumatic Fever, organized in 1944, consists of a group of representatives of all national medical organizations concerned with rheumatic fever. It operates administratively through the American Heart Association and carries out the program of the American Heart Association insofar as that relates to rheumatic fever.

Annual membership in the American Heart Association is $2.50 and includes twelve issues of *Modern Concepts of Cardiovascular Disease;* Journal membership is $10.00 and includes a year's subscription to the American Heart Journal (January-December), twelve issues of *Modern Concepts of Cardiovascular Disease*, and annual membership in the Association. Contributing membership starts at $25.00 per year; patron membership is $50.00 and over per year. Membership blanks will be sent upon request.

The Association earnestly solicits your support and suggestions for its work. Donations will be gratefully received and promptly acknowledged.

### Annual Meeting

The Annual Meeting and Twentieth Scientific Sessions of the American Heart Association will be held in Atlantic City, N. J., June 6 and 7, 1947. The Hotel President will be the headquarters for all meetings. On June 6, a meeting will be held with representatives of local Heart Associations to discuss the administrative structure of the American Heart Association with particular reference to program. The annual meeting of members will also be held on that day. The scientific sessions will take place on June 6 and 7. The annual dinner is scheduled for Saturday evening, June 7, at the Hotel President. Meetings begin at 9:00 A.M. each day, and members should plan to arrive on June 5. Hotel rooms will be in great demand and every member who wishes to attend is urged to make reservations immediately.

The chairman of the Program Committee for the Annual Scientific Sessions of the American Heart Association is Dr. Edgar V. Allen, Mayo Clinic, Rochester, Minn. All who desire to present papers at the meetings of June 6 and 7 in Atlantic City should forward to him an abstract of the proposed presentation of not more than 300 words. The deadline for the receipt of abstracts is March 30, 1947.